CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

89884

BIOEQUIVALENCY REVIEW(S)

JUN 24 1998

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA #89-8[redacted] APPLICANT: Hercon Laboratories, Inc.
ANDA #89-885
ANDA #89-884

DRUG PRODUCT: Nitroglycerin Transdermal System, 0.6 mg/hr, 0.4 mg/hr and 0.2 mg/hr

The Division of Bioequivalence has completed its review and has no further questions at this time. However, for the future applications, you are advised to submit data on the residual nitroglycerin contents in the used patches.

You should incorporate the dissolution testing into your manufacturing controls and stability program. The dissolution testing should be conducted in 500 mL of water at 32°C using paddle over disk at 50 rpm. The test product should meet the tentative dissolution specifications:

Sampling Schedule	Limits
0.25 hr	[redacted]
0.5 hr	[redacted]
1.0 hr	[redacted]
4.0 hr	[redacted]

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Nitroglycerin Transdermal System
AND #89-886; NTS, 0.6 mg/hr
AND #89-885; NTS, 0.4 mg/hr
AND #89-884; NTS, 0.2 mg/hr
Reviewer: Sikta Pradhan
XWP #89886SDW.N97

Hercon Laboratories, Co.
York, PA
Submission Date:
November 3, 1997
June 2, 1998

Review of a Bioequivalence Study, Dissolution Data and Waiver Requests

I. INTRODUCTION:

Nitroglycerin is used for the acute relief of angina pectoris. It is used for long term therapy of cardiac insufficiency and cardiac infarction. When given orally, nitroglycerin is extensively metabolized during its first pass, hence alternate routes of administration such as transdermal, are often used. Nitroglycerin transdermal delivery systems are developed in order to control the surface area of application, and the rate of drug delivery, thereby maintaining sustained plasma levels of nitroglycerin over an extended period of time.

This submission is a major amendment to the firm's conditionally approved AND of Nitroglycerin Transdermal System. The firm had previously conducted a bioequivalence study on this product (0.4 mg/hr strength patch). The study (submission dated December 8, 1994) was found unacceptable by the Agency. In this current amendment, the firm has included the data of a new bioequivalence study conducted on the test product (0.6 mg/hr strength patch). The firm has also informed the Agency that the patch size of the test product(s) has recently been increased. The current amendment also contains waiver requests for its 0.2 mg/hr and 0.4 mg/hr products.

Objective:

The objective of this Open-label, replicate design, two-treatment, four-period, randomized, crossover single dose study was to evaluate the bioequivalence of a re-sized (3.7% increased) Hercon's Nitroglycerin Transdermal System formulation relative to a commercially-available reference patch, Transderm-Nitro^{R} of Novartis.

In-Vivo Study:

The study was conducted in healthy, male volunteers under fasting conditions. The clinical study was conducted at under the supervision of Principal Investigator. The analytical study was conducted at

Study Dates:

Group I(subj. 28): 7/14/97, 7/18/97, 7/22/97, 7/26/97
Group II(subj. 21): 7/28/97, 8/1/97, 8/5/97, 8/9/97

Study Design:

A randomized, open-label, replicate design, two-treatment, four-period, crossover single dose bioequivalence study including a Hercon nitroglycerin patch formulation and a commercially available nitroglycerin reference patch manufactured by Novartis was conducted according to protocol # HERC-9701.

Subjects: Forty- nine (49) healthy male volunteers between 18-55 years of age and within ±15% of their ideal body weight according to Metropolitan Life Insurance Company Bulletin, 1983, were selected for the study after 1) Physical Examination, 2) Medical and Complete Routine Laboratory Tests (hematology, blood chemistry, urinalysis, etc.). The subjects were restricted from all medications for two weeks prior to the first drug administration until after the study was completed. The volunteers were not allowed to drink alcoholic beverages for 48 hours before dosing and throughout the period of sample collection.

Treatments:

A. Administration of a single Nitroglycerin Transdermal System, 0.6 mg/hr (111.9 mg/21.0 cm^2 patch) of the test formulation (Hercon), Lot # LO597NG/613; Potency: 99.6%, Lot size: patches; Duration of patch application 12 hrs.

B. Administration of a single Nitroglycerin Transdermal System, 0.6 mg/hr (75.0 mg/30 cm^2 patch) of the reference formulation (Transderm-Nitro^R, Novartis), Lot # 1F193881; Potency: 98.2%, Expiration Date: 7/99; Duration of patch application 12 hrs.

Dose Administration: Subjects were assigned to one of two treatment sequences (ABBA or BAAB) according to the randomization schedule. Each subject received two (2) treatments during the study with a 4-day washout period between them.

Drug Washout Period: Four days

Site of Patch Application: The skin at the site of application was clean and dry. Each patch was applied to the chest of each subject approximately halfway between the nipple and medio-clavicular line for 12 hours.

Vital signs: Vital signs such as, heart rate, blood-pressure, respiratory rate, etc. were determined periodically during the study. Times of measurement were: 0 (pre-dose), 0.5, 1, and 6 hours after application of each TNG-patch, and immediately after removal of each patch (12 hours post-dose). All vital sign measurements were taken within 10 minutes before or after the respective blood sampling.

Meal and Food Restrictions: All volunteers fasted for 8 hours prior to and 1 hours after drug administration. Fluids were restricted within one hour of dosing. Standard meal was served. No caffeine-containing food or beverage was served during the study.

Patch Removal:

The patch was removed within 5 minutes after collection of the 12-hour blood sample. Immediately after patch removed, the subject's skin was visually examined and rated for irritation. The patch from each individual subject was transferred into a protective pouch that was properly identified and sealed. Sealed pouches were sent to the sponsor for analysis of residual nitroglycerin content.

Blood Sample Collection:

Venous blood samples (5 ml) were collected in Vacutainer tubes containing sodiun heparin prior to dosing (0 time) and at 0.5, 1.0, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 12.5 and 13 hours after patch application. Plasma was separated and kept frozen at -70°C until analysis.

Assay Methodology:

Dates of Analysis: August 1, 1997 - September 5, 1997.

Method: Trinitroglycerin (TNG), 1,2 -dinitroglycerin (1,2-DNG) and 1,3 -dinitroglycerin (1,3-DNG) levels in plasma were estimated by method.

TNG, 1,2-DNG, and 1,3-DNG assay:

The calibration range, average correlation coefficient, overall percent coefficient of variation (%CV), and the number of analytical runs for each compound are summarized below:

Internal Standards: TNG-$^{15}N_3$, 1,2-DNG-$^{15}N_2$ and 1,3-DNG-$^{15}N_2$

Specificity: No interference was observed.

Linearity: The standard plots were linear in the concentration range of 0.01 ng/mL to 5.0 ng/mL for TNG and in the concentration range of 0.1 ng/mL to 10.0 ng/mL for 1,2-DNG and 1,3-DNG. The coefficient of determination of the calibration line was greater than 0.9996.

Sensitivity: The lower limit of quantitation (LLOQ) was 0.01 ng/mL for TNG and 0.10 ng/mL for both 1,2-DNG and 1,3-DNG; any value less than these was reported as zero.

Precision:

Within-study validation:
I. TNG
Interday Assay Precision from Standard Samples:
9.10% (CV) at 0.01 ng/mL; (N=45)
4.74% (CV) at 0.025 ng/mL; (N=49)
2.17% (CV) at 0.200 ng/mL; (N=49)
2.50% (CV) at 5.00 ng/mL; (N=49)
Interday Assay Precision from (QC) Control Samples:
(N=75)
6.38% (CV) at 0.025 ng/mL;
4.22% (CV) at 0.25 ng/mL;
3.26% (CV) at 4.00 ng/mL

II. 1,2-DNG
Interday Assay Precision from Standard Samples:
4.54% (CV) at 0.10 ng/mL; (N=50)
2.36% (CV) at 0.40 ng/mL; (N=50)
2.96% (CV) at 2.50 ng/mL; (N=50)
1.64% (CV) at 10.00 ng/mL; (N=49)
Interday Assay Precision from (QC) Control Samples:
4.71% (CV) at 0.25 ng/mL; (N=77)
4.72% (CV) at 1.50 ng/mL; (N=77)
3.33% (CV) at 8.00 ng/mL; (N=76)

III. 1,3-DNG
Interday Assay Precision from Standard Samples:
5.46% (CV) at 0.10 ng/mL; (N=50)
2.11% (CV) at 0.40 ng/mL; (N=50)
2.33% (CV) at 2.50 ng/mL; (N=50)
1.98% (CV) at 10.00 ng/mL; (N=49)
Interday Assay Precision from (QC) Control Samples:
5.00% (CV) at 0.25 ng/mL; (N=77)
4.63% (CV) at 1.50 ng/mL; (N=77)
3.21% (CV) at 8.00 ng/mL; (N=76)

Stability:

1. Frozen control samples were found to be stable through three freeze/thaw cycles for TNG, 1,2-DNG and 1,3-DNG. The test samples were compared with freshly thawed (once only) samples.

2. Frozen control samples for TNG, 1,2-DNG and 1,3-DNG were stable for at least forty weeks at -70°C.

3. Quality control samples for TNG, 1,2-DNG and 1,3-DNG were found to be stable at room temperature for 4 hours.

4. The firm did not provide the short term stability data at 0-4°C for TNG, 1,2-DNG and 1,3-DNG. However, the overall stability data are acceptable.

Results:

Forty-nine (49) male volunteers were enrolled in the study and 46 of them completed all phases of the study. The ANOVA analysis was conducted on 46 subjects. Subject# 33 withdrew from the study due

to adverse events such as headache, nausea, etc., and Subject #44 became tired of blood draws and voluntarily withdrew from the study prior to period 2. Subject# 45 was absent for period 2 of the study. A total of 25 different adverse events and the observed patch irritations were reported in Table 1A and 1B (attached). None of these adverse events reported were considered to be severe. All vital signs occurred during the study were measured and reported in the Appendix A (attached). The firm has reported, no clinically significant changes in clinical laboratory test results, physical examinations, or ECGs occurred during the study. It has been reported by the firm that no treatment effects were observed for the adverse events. Mean plasma TNG, 1,2-DNG and 1,3-DNG levels are presented in Tables 2(and Fig.1&2), 3(and Fig.3&4) and 4(and Fig.5&6), respectively.

Table 2

Mean Plasma TNG Levels (pg/mL)

Time (hour)	Reference (B_1) N = 46	Reference (B_2) N = 46	Test (A_1) N = 46	Test (A_2) N = 46
Pre-dose	0	0	0	0
0.5	107.18(89)*	139.82(120)	65.69(127)	115.80(103)
1.0	194.61(65)	263.58(84)	146.38(83)	258.89(79)
1.5	168.66(56)	207.69(69)	169.82(100)	220.53(69)
2.0	222.04(72)	222.00(57)	169.13(62)	285.05(77)
2.5	165.49(58)	191.96(55)	138.50(61)	251.71(72)
3.0	197.53(72)	200.44(56)	186.97(80)	250.65(70)
4.0	254.56(79)	271.42(66)	214.50(67)	355.29(80)
5.0	232.80(59)	251.05(52)	224.24(78)	352.41(74)
6.0	226.28(57)	261.61(58)	262.07(96)	417.23(135)
8.0	283.25(72)	226.82(48)	232.12(71)	337.87(85)
10.0	232.10(61)	229.54(53)	236.53(66)	310.12(62)
12.0	172.44(80)	175.94(60)	163.34(61)	222.49(68)
12.5	18.31(61)	18.23(58)	31.32(64)	39.00(67)
13.0	4.82(184)	6.0413(135)	43.25(384)	15.68(81)

* Coefficient of Variation; N = Total Number of Subjects

Table 3
Mean Plasma 1,2-DNG Levels (ng/mL)

Time (hour)	Reference (B_1) N = 46	Reference (B_2) N = 46	Test (A_1) N = 46	Test (A_2) N = 46
Pre-dose	0	0	0	0
0.5	0.51(99)	0.60(111)	0.26(124)	0.46(101)
1.0	1.84(60)	2.09(63)	1.19(78)	1.94(68)
1.5	2.71(48)	3.02(49)	2.00(64)	3.01(62)
2.0	3.21(42)	3.46(39)	2.52(55)	3.75(57)
2.5	3.43(38)	3.76(35)	2.91(52)	4.32(57)
3.0	3.39(37)	3.70(35)	3.00(49)	4.38(55)
4.0	3.63(35)	3.90(34)	3.37(45)	4.75(54)
5.0	3.77(32)	4.09(34)	3.65(43)	5.29(57)
6.0	3.97(33)	4.28(31)	3.92(43)	5.39(52)
8.0	3.81(35)	3.94(33)	3.78(41)	5.20(54)
10.0	3.90(35)	4.19(33)	4.07(39)	5.42(50)
12.0	3.63(35)	3.98(32)	3.78(39)	4.94(50)
12.5	2.38(30)	2.55(26)	2.62(34)	3.23(40)
13.0	1.39(34)	1.45(29)	1.57(44)	1.86(40)

* Coefficient of Variation
N = Total Number of Subjects

Table 4
Mean Plasma 1,3-DNG Levels (ng/mL)

Time (hour)	Reference (B_1) N = 46	Reference (B_2) N = 46	Test (A_1) N = 46	Test (A_2) N = 46
Pre-dose	0	0	0	0
0.5	0.06(158)	0.087(138)	0.03(215)	0.07(141)
1.0	0.36(59)	0.40(61)	0.21(87)	0.36(66)
1.5	0.54(47)	0.59(48)	0.39(58)	0.55(56)
2.0	0.65(43)	0.68(40)	0.49(49)	0.68(51)
2.5	0.71(39)	0.77(38)	0.57(46)	0.78(49)
3.0	0.73(40)	0.78(36)	0.61(43)	0.82(49)
4.0	0.76(36)	0.81(37)	0.66(39)	0.87(47)
5.0	0.74(34)	0.80(35)	0.67(40)	0.91(48)
6.0	0.75(34)	0.80(34)	0.70(41)	0.93(49)
8.0	0.74(36)	0.77(35)	0.70(40)	0.92(49)
10.0	0.73(38)	0.78(38)	0.73(41)	0.92(47)
12.0	0.72(39)	0.78(35)	0.71(41)	0.89(48)
12.5	0.54(35)	0.57(33)	0.56(36)	0.71(51)
13.0	0.36(39)	0.37(33)	0.37(33)	0.45(39)

* Coefficient of Variation
N = Total Number of Subjects

The mean pharmacokinetic parameters derived from the plasma data are presented in Tables 5-7.

Table 5

Mean Pharmacokinetic Parameters for Plasma TNG

Parameters	Test(A) NOT-FA (21.0 cm^2) of Hercon N=46 Mean±SD	Reference(B) Transderm-Nitro® (Novartis) N=46 Mean±SD	Ratio A/B	90% C.I. Based on LSM. N=46
AUC_{0-T} (pg.hr/mL)	3087.66±2225.3 LSM:3038.42	2690.03±1382.5 LSM: 2581.37		
AUC_{0-inf} (pg.hr/mL)	3154.01 ± 2245.7 LSM: 3049.22	2806.16 ± 1410.6 LSM: 2585.86		
C_{max} (pg/mL)	460.16 ± 458.0 LSM: 454.93	380.70 ± 224.5 LSM: 358.55		
Css (pg/mL)	271.61 ± 197.5 LSM: 267.29	236.81 ± 12 LSM: 227.01		
T_{max} (hour)	6.02 ± 2.6	4.77 ± 2.92		
KE (1/hour)	2.763 ± 0.99	3.655 ± 1.22		
t1/2 (hour)	0.29 ± 0.13	0.21 ± 0.08		
%Fluctuation	110.7 ± 40.0	109.7 ± 56.75		
$LnAUC_{0-T}$ Geometric mean	7.82081 2491.92	7.75575 2334.96	1.07	100; 114
$LnAUC_{0-inf}$ Geometric mean	7.82878 2511.86	7.77069 2370.11	1.06	99; 114
LnC_{max} Geometric mean	5.84212 344.51	5.77310 321.53	1.07	98; 117

N = Total Number of Subjects

Table 6

Mean Pharmacokinetic Parameters for Plasma 1,2-DNG

Parameters	Test(A) NOT-FA (21.0 cm^2) of Hercon N=46 Mean±SD	Reference(B) Transderm-Nitro® (Novartis) N=46 Mean±SD	Ratio A/B	90% C.I. Based on LSM. N=46
AUC_{0-T} (ng.hr/mL)	49.67 ± 25.79 LSM: 49.77	44.89 ± 14.81 LSM: 43.87		
AUC_{0-inf} (ng.hr/mL)	51.75 ± 26.28 LSM: 51.50	46.38 ± 14.99 LSM: 45.37		
C_{max} (ng/mL)	5.04 ± 2.62 LSM: 4.68	4.42 ± 1.40 LSM: 4.33		
Css (ng/mL)	4.67 ± 2.40 LSM: 4.68	4.12 ± 1.32 LSM: 4.02		
T_{max} (hour)	8.20 ± 2.27	7.48 ± 2.79		
KE (1/hour)	0.920 ± 0.22	0.986 ± 0.17		
t1/2 (hour)	0.79 ± 0.19	0.73 ± 0.15		
%Fluctuation	32.21 ± 10.45	29.65 ± 25.51		
$LnAUC_{0-T}$ Geometric mean	3.79267 44.37	3.73733 41.99	1.06	101; 111
$LnAUC_{0-inf}$ Geometric mean	3.82948 46.04	3.77305 43.51	1.06	101; 111
LnC_{max} Geometric mean	1.51004 4.53	1.42724 4.17	1.09	104; 114

N = Total Number of Subjects

Table 7

Mean Pharmacokinetic Parameters for Plasma 1,3-DNG

Parameters	Test(A) NOT-FA (21.0 cm^2) of Hercon N=46 Mean±SD	Reference(B) Transderm-Nitro® (Novartis) N=46 Mean±SD	Ratio A/B	90% C.I. Based on LSM. N=46
AUC_{0-T} (ng.hr/mL)	9.03 ± 4.32 LSM: 9.00	8.83 ± 3.15 LSM: 8.64		
AUC_{0-inf} (ng.hr/mL)	9.73 ± 4.44 LSM: 9.64	9.43 ± 3.19 LSM: 9.20		
C_{max} (ng/mL)	0.88 ± 0.40 LSM: 0.87	0.85 ± 0.30 LSM: 0.84		
Css (ng/mL)	0.84 ± 0.40 LSM: 0.84	0.80 ± 0.28 LSM: 0.79		
T_{max} (hour)	8.01 ± 2.60	6.20 ± 3.02		
KE (1/hour)	0.66 ± 0.22	0.73 ± 0.16		
t1/2 (hour)	1.16 ± 0.38	1.01 ± 0.27		
%Fluctuation	22.44 ± 7.30	24.28 ± 25.36		
$LnAUC_{0-T}$ Geometric mean	2.09334 8.112	2.09892 8.157	0.99	95; 103
$LnAUC_{0-inf}$ Geometric mean	2.16999 8.76	2.16767 8.74	1.00	96; 104
LnC_{max} Geometric mean	-0.22793 0.796	-0.23158 0.793	1.00	97; 104

N = Total Number of Subjects

Statistical Analysis:

The firm has included a term for simple first-order residual (carryover) effects in their statistical model without giving any reason. The Model used was:

T = sequence + group + sequence*group + subject(sequence*group) + period(group) + treatment + treatment*group + residual

A reduced ANOVA model excluding the group-by-treatment interaction term (when this term was not significant) was then employed to evaluate the bioequivalence of the pharmacokinetic parameters of interest.

However, according to the Agency statistician's opinion, if the first-order residual effects are to be considered, the sponsor's model is inadequate to examine all of the possible residual effects. The sponsor's experimental design (as shown below) with four periods and two sequences was carried out in two groups of subjects. However, the group structure of the study does not affect the issues involving possible residual effects.

	Periods			
	1	2	3	4
Sequence 1	T	R	R	T
Sequence 2	R	T	T	R

The sponsor's model incorrectly assumed that the effect of T on T was the same as the effect of T on R, and that the effect of R on T was the same as the effect of R on R.

Regarding the residual effect, one possible cause is direct carryover of the drug substance from one period into the next. There is essentially no evidence of such direct carryover in this study, with the time zero concentrations of the parent compound, the 1,2 metabolite, and the 1,3 metabolite reported as 0 for all subjects and periods except for subject 47, period 1, and subject 48, period 1. In those two cases, the time zero concentrations are reported as missing.

reported as missing.

Since the Division has not yet developed definitive procedures to analyze the residual effect, and the Agency has previously approved applications on Nitroglycerin Transdermal Patches, where the pharmacokinetic data were analyzed using a statistical model of replicate design without including a term for residual, the data of the current application were also reanalyzed using a similar model by the Agency statistician and found acceptable. The study data of all three analytes met the usual bioequivalence criterion of 80- 125% for 90% CI for all three PK parameters, AUCt, Cmax, and AUCinf as shown below:

	Parent compound	1.2 Metabolite	1.3 Metabolite
LnAUCt	99.60% , 113.39%	99.75% , 109.06%	94.50% , 102.46%
LnCmax	97.58% , 115.68%	102.60% , 112.06%	95.43% , 102.89%
LnAUCinf	98.70% , 112.94%	100.19% , 109.33%	95.59% , 103.37%

Dissolution:

The dissolution (drug release) testing data are presented in Table 8 below:

Table 8. In Vitro Dissolution Testing (drug release)

Drug: NTS-FA Transdermal System
Dose Strengths: 0.6 mg/hr (21.0 cm^2 patch)
AND No.: 89-886-
Firm: Hercon Lab.
Submission Date: November 3, 1997

I. Conditions for Dissolution Testing:

USP XXIII Paddle (USP modified Apparatus 5, paddle over disk) RPM: 50
No. Units Tested: 12
Medium: Water at 32 °C; Volume: 500 mL
Specifications: Has been proposed
Reference Drug: Transderm-Nitro ® (0.6 mg/hr); Label Claim: 75 mg/30 cm. sq.
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Hour)	Test Product:Patch Lot # LO597NG/613 Strength 0.6 mg/hr; 111.9 mg /21cm^2			Reference Product: Patch Lot # 1F193881 Strength 0.6 mg/hr ; 75.0 mg/30 cm^2		
	Mean %	Range	%CV	Mean %	Range	%CV
0.25	41.0		3.6	3.8		3.3
0.5	61.0		1.6	4.4		2.8
1	76.0		1.8	5.6		2.5
2	82.9		1.9	8.0		2.5
4	83.5		3.6	12.5		2.4
Sampling Times (Hour)	Test Product: Patch Lot # LANG/612 Strength 0.4 mg/hr; 74.6 mg/14.0 cm^2			Reference Product: Patch Lot # 1M205516 Strength 0.4 mg/hr ; 50.0 mg/20 cm^2		
0.25	37.4		4.2	3.4		1.7
0.5	57.6		4.4	4.2		1.1
1	74.0		3.1	5.5		1.3
2	83.0		2.9	7.7		1.5
4	87.9		2.0	11.9		1.7

Sampling Times (Hour)	Test Product: Patch Lot # LANG/614 Strength 0.2 mg/hr; 37.3 mg/ 7 cm ^{2}			Reference Product: Patch Lot #1M010951 Strength 0.2 mg/hr ; 25.0 mg/10 cm ^{2}		
0.25	36.3		5.2	3.4		2.5
0.5	57.6		5.8	4.2		2.2
1	75.2		4.3	5.6		2.4
2	85.9		2.9	7.5		1.9
4	90.5		2.3	11.4		2.1

Formulations:

The compositions of three proposed strengths of Hercon's Nitroglycerin Transdermal System are presented below:

AND		Strength		Old Size		New Size
AND #89-884		0.2 mg/hr		6.75 cm^2		7.0 cm^2
AND #89-885		0.4 mg/hr		13.5 cm^2		14.0 cm^2
AND #89-886		0.6 mg/hr		20.25 cm^2		21.0 cm^2

Components	Strengths		
Delivery Rate	0.2 mg/hr	0.4 mg/hr	0.6 mg/hr
Patch size	7.0 cm^2	14.0 cm^2	21.0 cm^2
Nitroglycerin	37.3 mg	74.7 mg	111.9 mg
Adhesive Polymer	13.6 mg	26.2 mg	39.3 mg
Adhesive Polymer	16.6 mg	32.04 mg	48.01 mg
Backing Film	7.0 cm^2	14.0 cm^2	21.0 cm^2
Coated Reservoir Weight	**68.9 mg**	**132.9 mg**	**199.2 mg**

Comments:

1. For nitroglycerin (TNG), 1,2-dinitroglycerin and 1,3-dinitroglycerin of the test product, the 90% confidence interval for $LnAUC_T$, $LnAUC_{0-inf}$ and LnC_{MAX} were within the 80% to 125% limit.

2. The firm has also conducted an acceptable skin irritation study.

3. The dissolution (drug release) testing conducted by Hercon Laboratories on its Nitroglycerin Transdermal System Face Adhesive Patch, 0.6 mg/ml, Lot #LO597NG/613 comparing it to Transderm-Nitro®, 0.6 mg/hr, Lot #1F193881 manufactured by Novartis has been found acceptable.

   The tentative specifications for the test product should be:

Sampling Schedule	Limits
0.25 hr	%
0.5 hr	%
1.0 hr	%
4.0 hr	%

4. The dissolution (drug release) data of 0.2 mg/hr and 0.4 mg/hr patches are acceptable. The formulations for the 0.2 mg/hr and 0.4 mg/hr strengths are proportionally similar to the 0.6 mg/hr patch, and therefore, the waivers on 0.2 mg/hr and 0.4 mg/hr patches are granted.

Recommendations:

1. The in vivo bioequivalence study conducted by Hercon Laboratories on its Nitroglycerin Transdermal System Face Adhesive Patch (111.9 mg /21.0 cm^2) of 0.6 mg/hr, Lot #LO597NG/613 comparing it to Transderm-Nitro^R patch (75 mg/30 cm^2) of 0.6 mg/hr, Lot #1F193881 manufactured by Novartis has been found acceptable by the Division of Bioequivalence. The study demonstrates that Hercon's Nitroglycerin Transdermal System Face Adhesive Patch (111.9 mg /21.0 cm^2) of 0.6 mg/hr is bioequivalent to the reference product, Transderm-Nitro^R Patch (75 mg /30 cm^2) of 0.6 mg/hr.

2. The dissolution (drug release) testing conducted by Hercon Laboratories on its Nitroglycerin Transdermal System Face Adhesive Patch, 0.6 mg/ml, Lot #LO597NG/613 comparing it to Transderm-Nitro^R, 0.6 mg/hr, Lot #1F193881 manufactured by Novartis has been found acceptable.

   The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 500 mL of water at 32°C using paddle over disk at 50 rpm. The test product should meet the tentative dissolution specifications:

Sampling Schedule	Limits
0.25 hr	[%
0.5 hr	%
1.0 hr	%
4.0 hr	%]

3. The firm has also conducted an acceptable skin irritation study.

4. The dissolution (drug release) testings conducted by Hercon Laboratories on its Nitroglycerin Transdermal System Face Adhesive Patches of 0.2 mg/hr (37.3 mg /7.0 cm^2), Lot #L0557NG/614, and 0.4 mg/hr (74.6 mg/14.0 cm^2), #LANG/612 are acceptable. The formulations for the 0.2 mg/hr and 0.4 mg/hr strengths are proportionally similar to the 0.6 mg/hr patch of the test product which underwent bioequivalency testing. The

waivers of in vivo bioequivalence study requirements for the 0.2 mg/hr (37.3 mg /7.0 cm^2) and 0.4 mg/hr (74.6 mg /14.0 cm^2) patches of the test product are granted.

/S/

Sikta Pradhan, Ph. D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHUANG
FT INITIALED YCHUANG /S/ 6/17/98

Concur: /S/ Date: 6/18/98
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

cc: AND # 89-886 (original, duplicate), HFD-652 (Huang, Pradhan), HFD-650 (Director),Drug File, Division File.

Table - 1(a)

NUMBER OF SUBJECTS REPORTING ADVERSE EVENTS FOR THE DIFFERENT TREATMENTS

Adverse Event	Test Formulation	Reference Formulation
Body Aches	1	-
Burning at Patch Site	4	2
Chest Pain	1	-
Chest Tightness	-	1
Cold Sensation	1	1
Dizziness	1	1
Drowsiness	1	-
Emesis	-	4
Erythema at Dose Site	2	2
Fatigue	6	2
Headache	89	88
Indigestion	1	-
Irritation at Patch Site	2	1
Leg Pain	-	1
Lightheadedness	2	3
Nausea	6	9
Neck Pain	1	-
Neck Pressure	-	1
Neck Tension	-	2
Pain at Patch Site	-	1
Painful Eyes	1	-
Sensation of Swollen Throat	-	1
Stomach Ache	1	-
Syncope	1	-
Weakness	-	1

Table - 1(b)

OBSERVED PATCH IRRITATIONS

Time Point	Test Formulation			Reference Formulation		
	Absent	Mild	Moderate	Absent	Mild	Moderate
Immediately Following Patch Removal	14	72	6	4	68	23
1 Hour Following Patch Removal	89	3	0	86	7	0
2 Hours Following Patch Removal	91	1	0	87	6	0

Figure 1

Trinitroglycerin

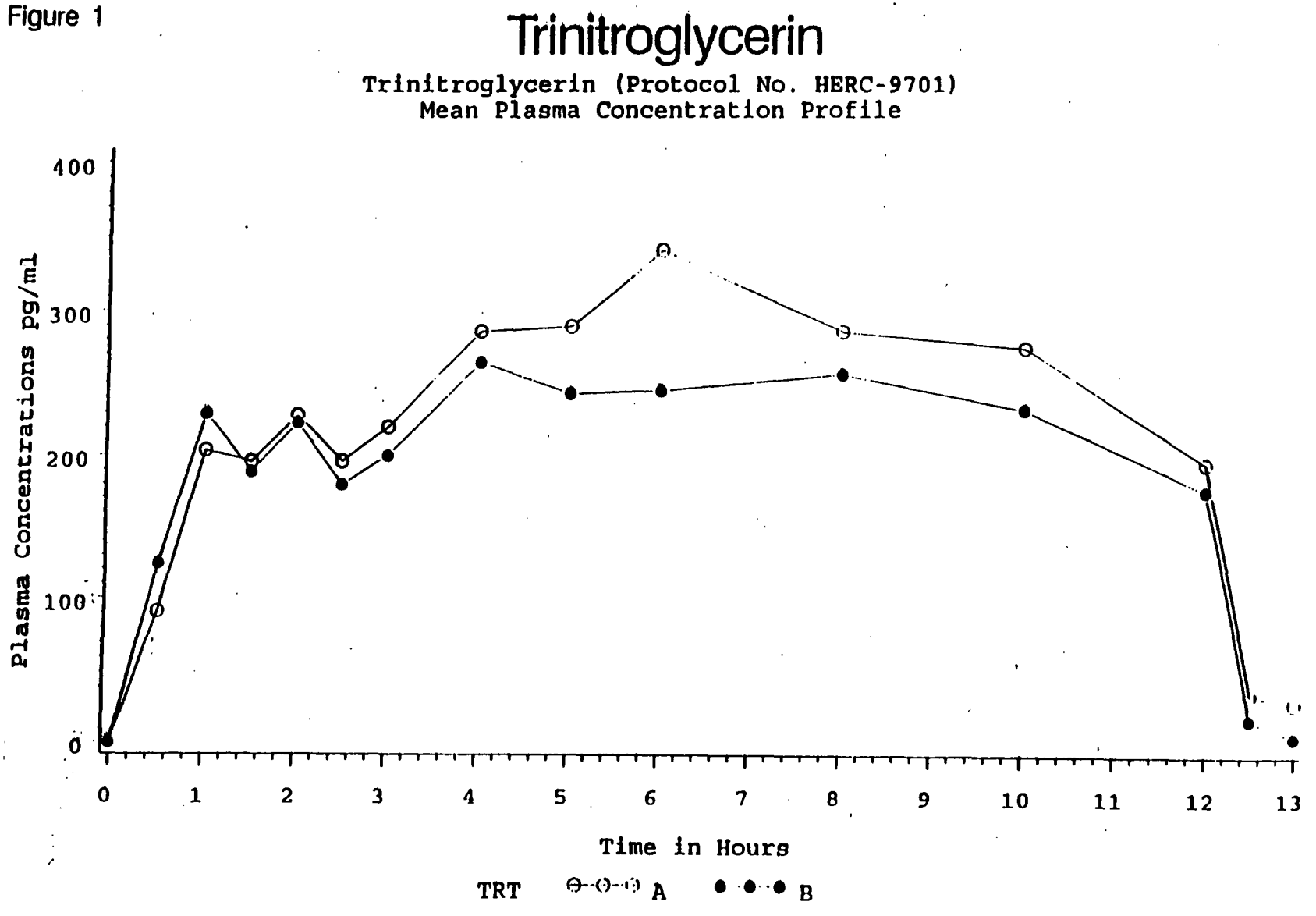

Figure 2

Trinitroglycerin

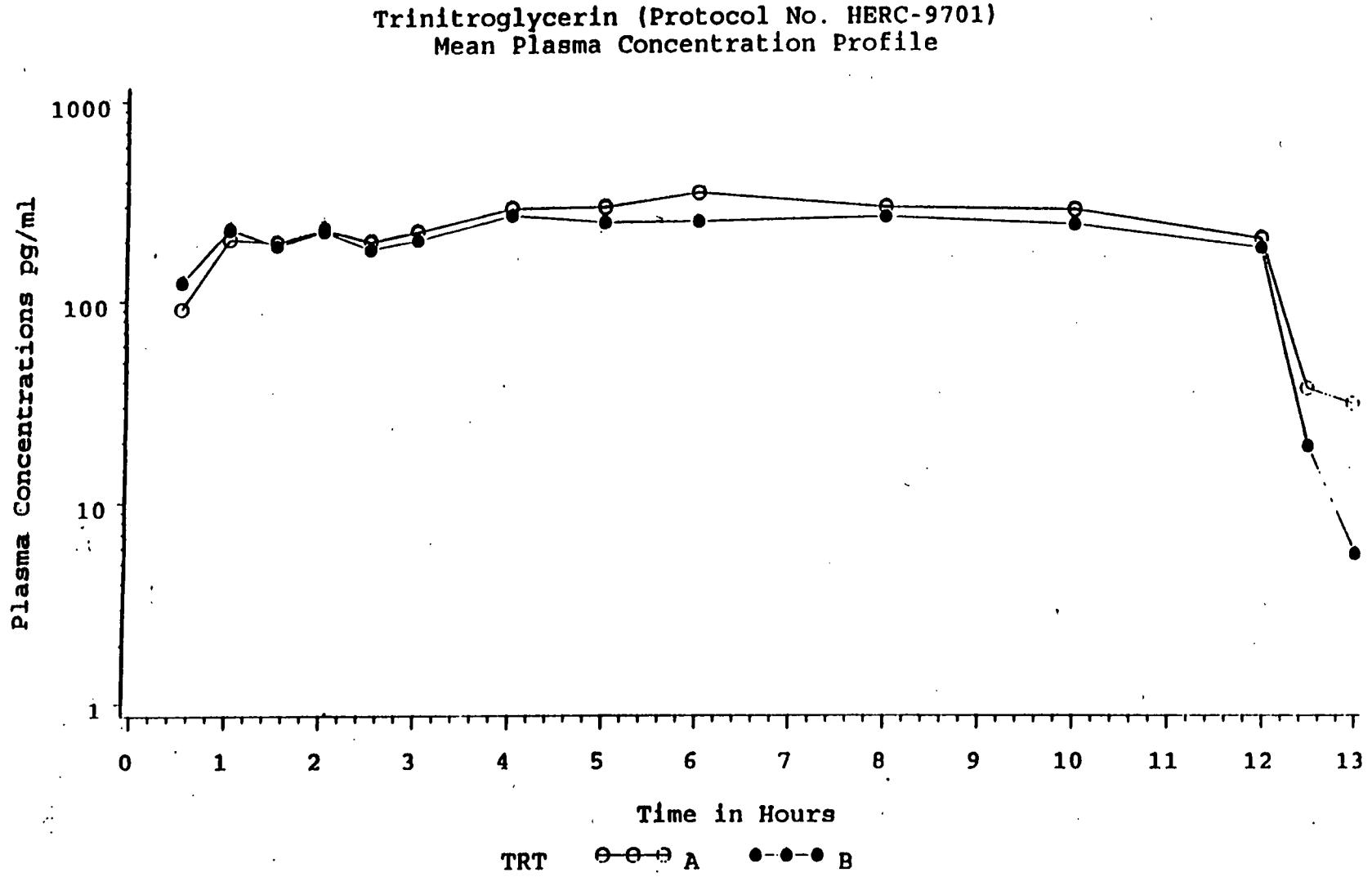

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Figure 3

1,2—Dinitroglycerin

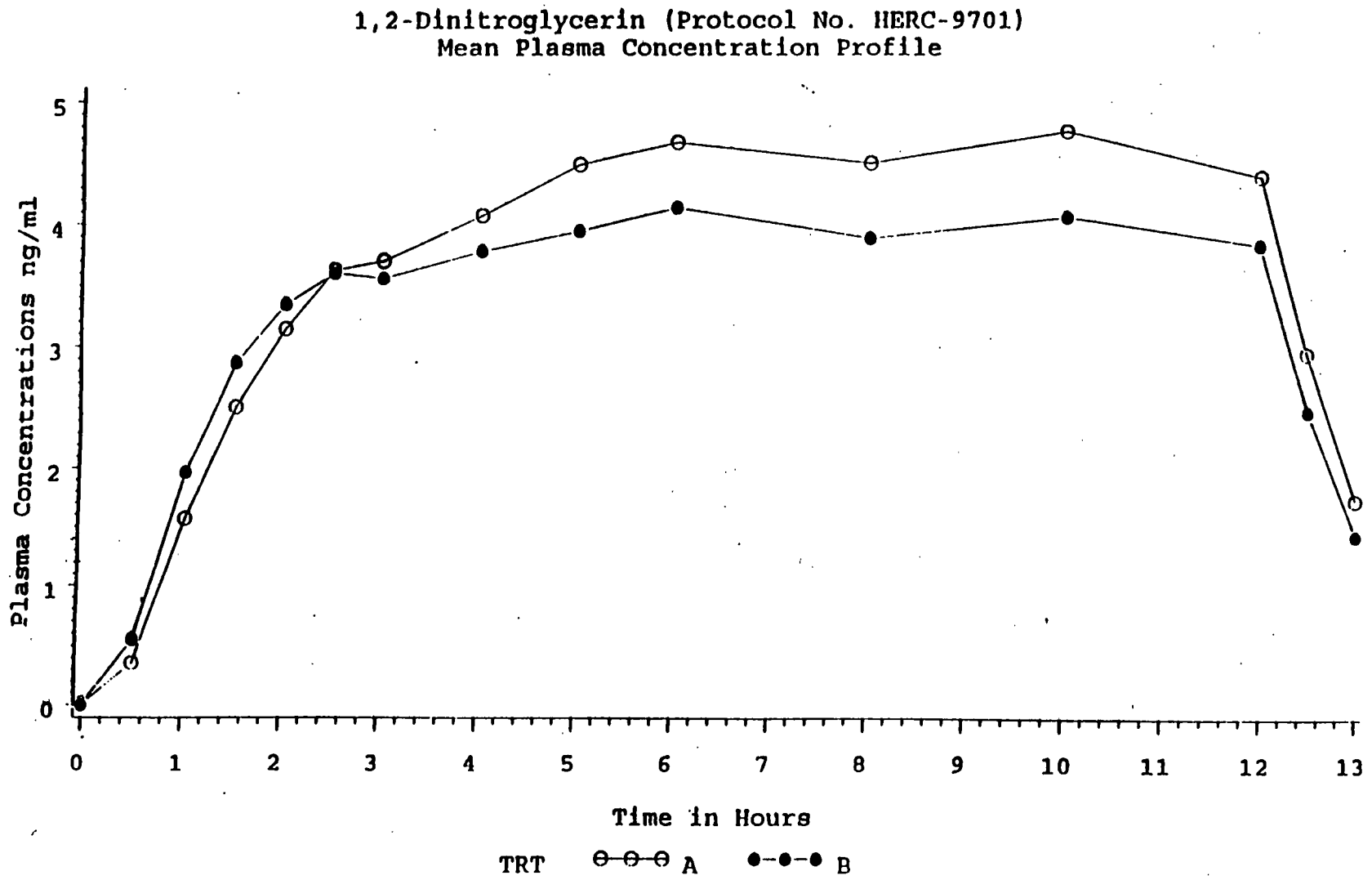

Figure 4

1,2–Dinitroglycerin

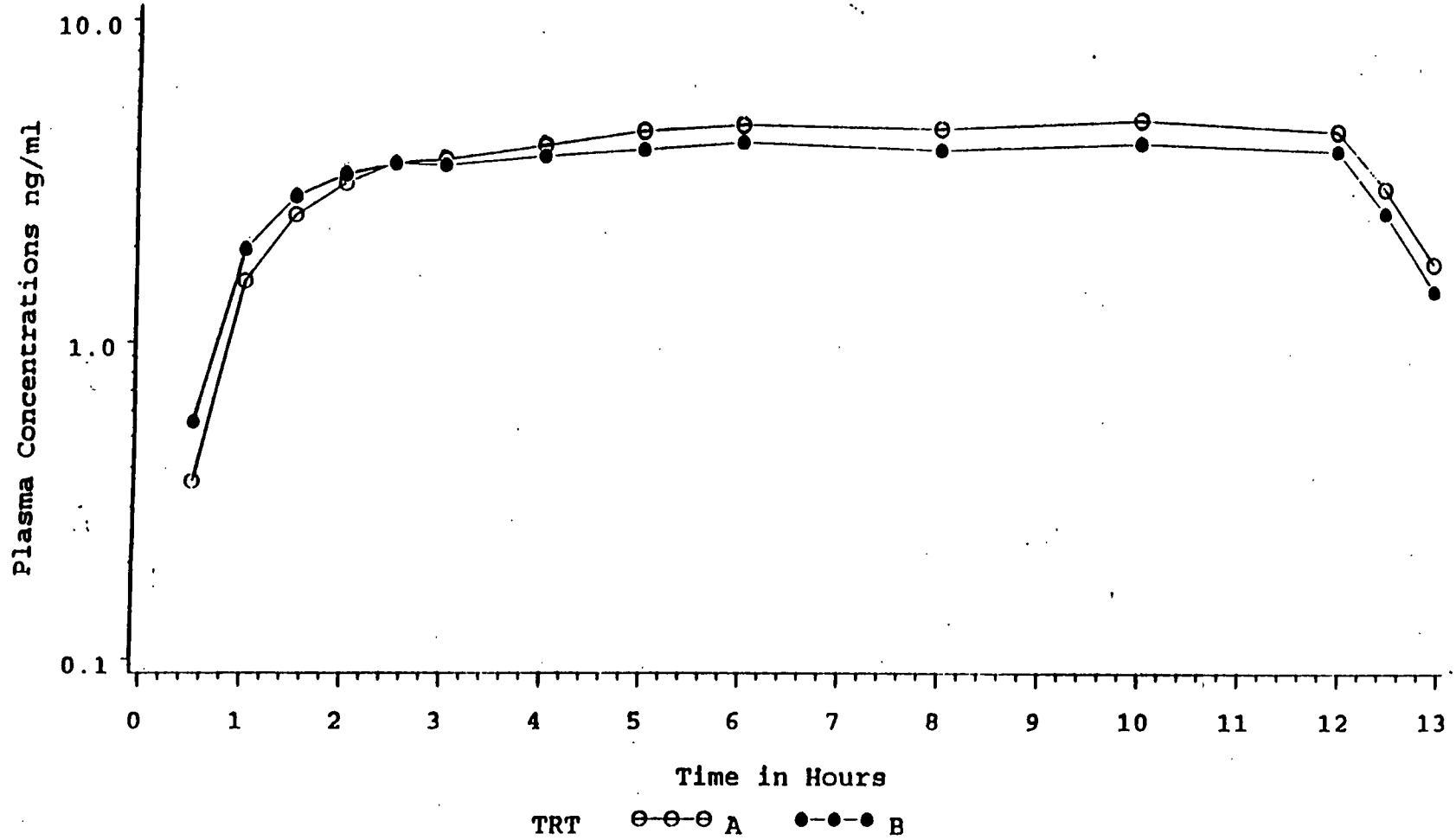

Figure 5

1,3 – Dinitroglycerin

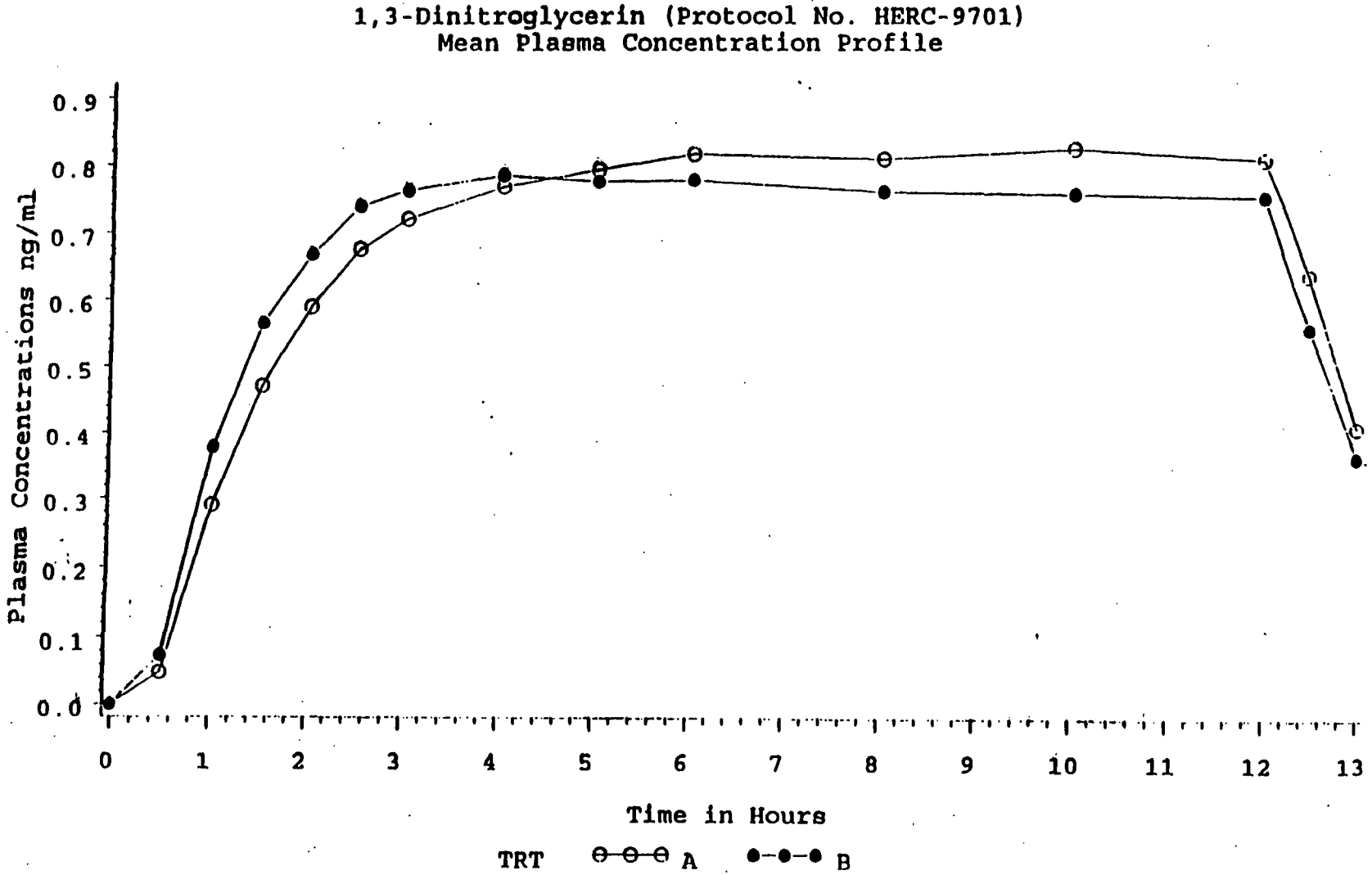

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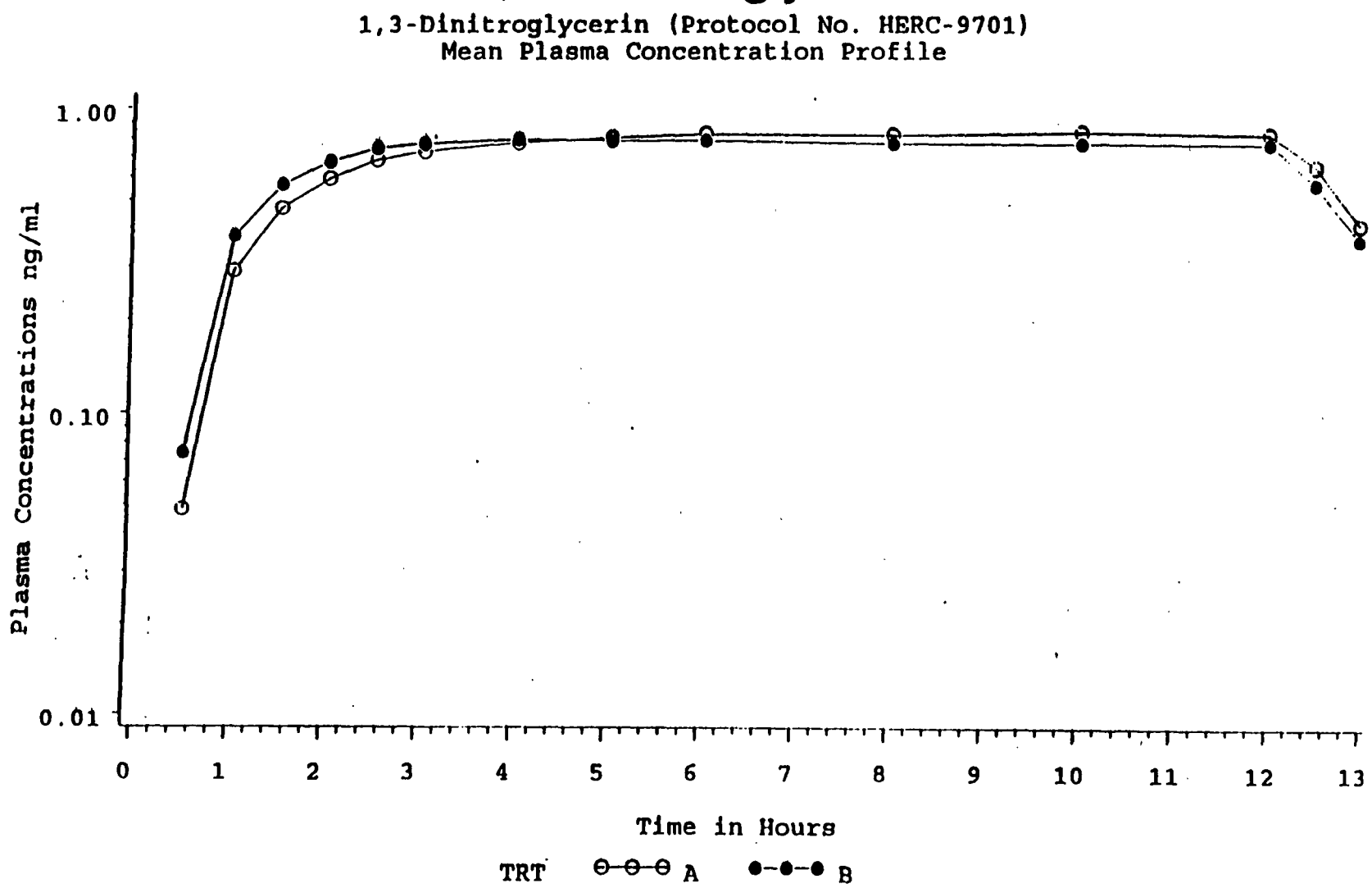
Figure 6

1,3 – Dinitroglycerin



ATTACHMENT #1

VITAL SIGNS OUTPUT

SUMMARY STATISTICS FOR VITAL SIGNS AT EACH SAMPLING POINT (BY TREATMENT)

Hercon Laboratories, Inc.
Nitroglycerin (Protocol No. Herc9701)
Fasting Single-Dose In Vivo Bioequivalence Study
Arithmetic Mean of Vital Signs
Versus Time (CV%) in 46 Subjects

VITSIGN=' DIASTOLIC'

Time	Reference Treatment B1	Reference Treatment B2	Test Treatment A1	Test Treatment A2	Ratio (A1+A2/B1+B2)
0	80.3(8.7%)	79.1(10.0%)	81.7(9.3%)	79.0(10.0%)	1.008
0.5	80.4(9.1%)	80.8(11.1%)	79.2(9.3%)	80.0(10.9%)	0.988
1	80.5(12.7%)	74.6(13.0%)	80.7(9.8%)	78.9(10.8%)	1.017
2	79.0(7.5%)	76.9(12.6%)	79.2(10.1%)	78.4(9.9%)	1.011
4	79.0(8.6%)	76.0(10.8%)	78.7(11.2%)	78.0(10.0%)	1.011
8	74.3(9.8%)	71.2(11.7%)	73.4(9.4%)	71.2(10.6%)	0.994
12	75.7(12.8%)	73.3(12.8%)	75.2(10.8%)	74.5(12.7%)	1.005
13	73.3(8.8%)	72.3(9.0%)	70.7(8.3%)	73.5(11.5%)	0.990

VITSIGN=' SYSTOLIC'

Time	Reference Treatment B1	Reference Treatment B2	Test Treatment A1	Test Treatment A2	Ratio (A1+A2/B1+B2)
0	111.8(8.5%)	111.5(7.8%)	115.1(9.2%)	109.0(7.5%)	1.004
0.5	107.5(8.3%)	109.3(7.6%)	111.2(10.9%)	108.3(9.3%)	1.012
1	107.5(9.6%)	103.9(8.6%)	110.8(9.1%)	103.9(9.1%)	1.016
2	105.1(10.5%)	102.7(8.7%)	105.1(9.4%)	101.7(7.6%)	0.995
4	105.4(9.8%)	103.1(9.7%)	106.7(9.3%)	106.1(9.6%)	1.021
8	104.9(9.3%)	104.0(9.8%)	104.3(9.1%)	106.0(10.4%)	1.007
12	113.9(9.1%)	109.6(11.0%)	112.0(8.3%)	112.5(9.4%)	1.005
13	113.7(8.8%)	112.7(8.5%)	112.0(8.7%)	115.1(10.9%)	1.003

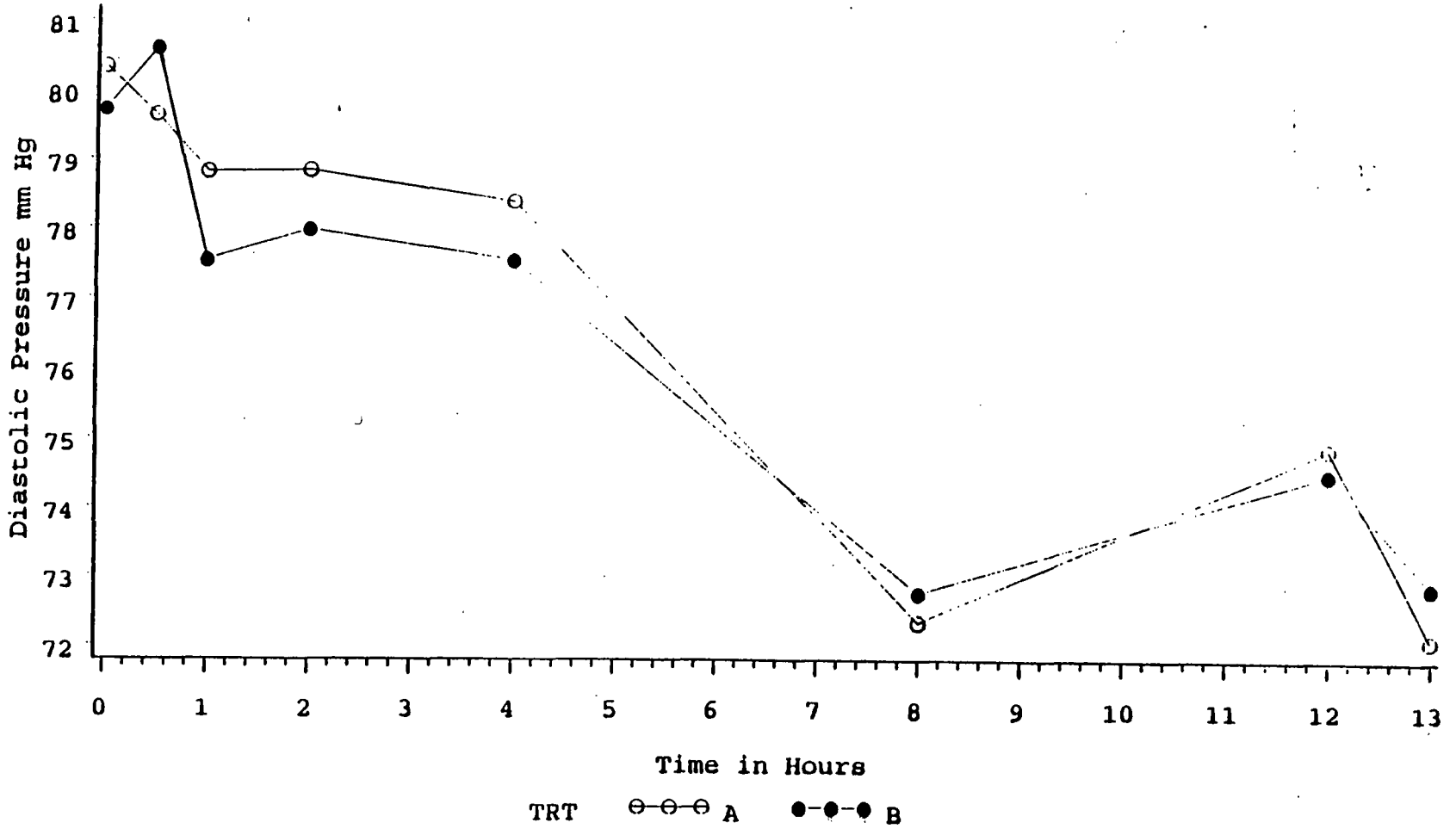
VITSIGN=PULSE

Time	Reference Treatment B1	Reference Treatment B2	Test Treatment A1	Test Treatment A2	Ratio (A1+A2/B1+B2)
0	61.8(11.7%)	62.8(11.9%)	61.8(15.2%)	63.2(11.8%)	1.003
0.5	64.4(13.9%)	66.0(13.4%)	65.7(13.4%)	64.4(12.2%)	0.998
1	66.0(13.8%)	68.7(15.5%)	64.0(15.1%)	69.4(13.7%)	0.990
2	65.1(10.6%)	68.7(12.0%)	64.7(12.1%)	69.6(12.0%)	1.004
4	76.7(12.7%)	77.2(14.5%)	76.5(12.9%)	79.3(12.6%)	1.013
8	69.7(13.4%)	69.2(12.1%)	68.0(11.4%)	69.3(13.4%)	0.989
12	74.8(11.9%)	71.7(13.9%)	74.1(11.1%)	73.5(14.2%)	1.008
13	70.0(12.2%)	71.2(10.9%)	70.4(9.9%)	70.2(11.3%)	0.996

MEAN AND INDIVIDUAL DIASTOLIC BLOOD PRESSURE PROFILES

Hercon Laboratories, Inc.

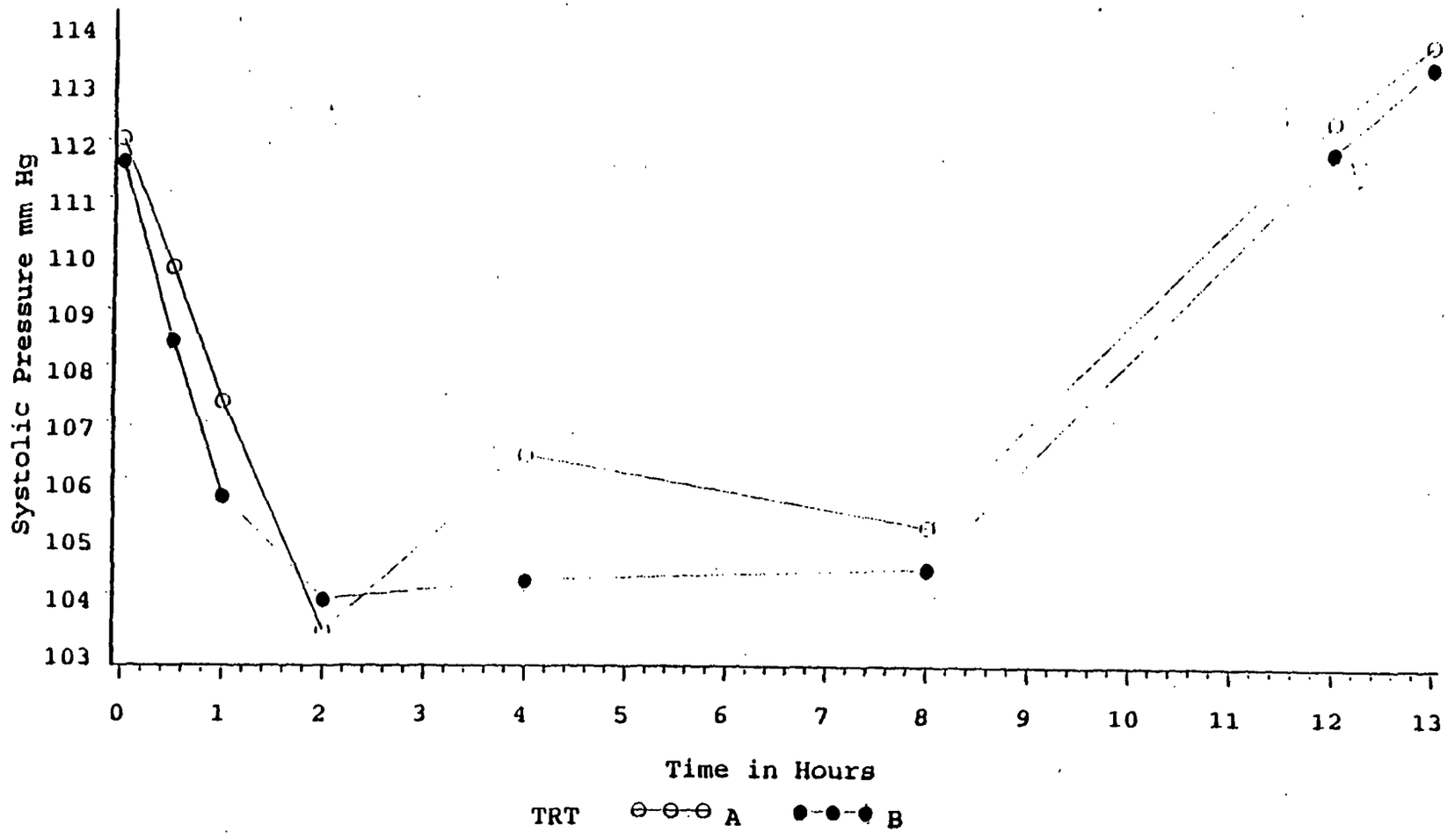
Nitroglycerin (Protocol No. Herc9701)
Mean Blood Pressure Profiles



MEAN AND INDIVIDUAL SYSTOLIC BLOOD PRESSURE PROFILES

Hercon Laboratories, Inc.

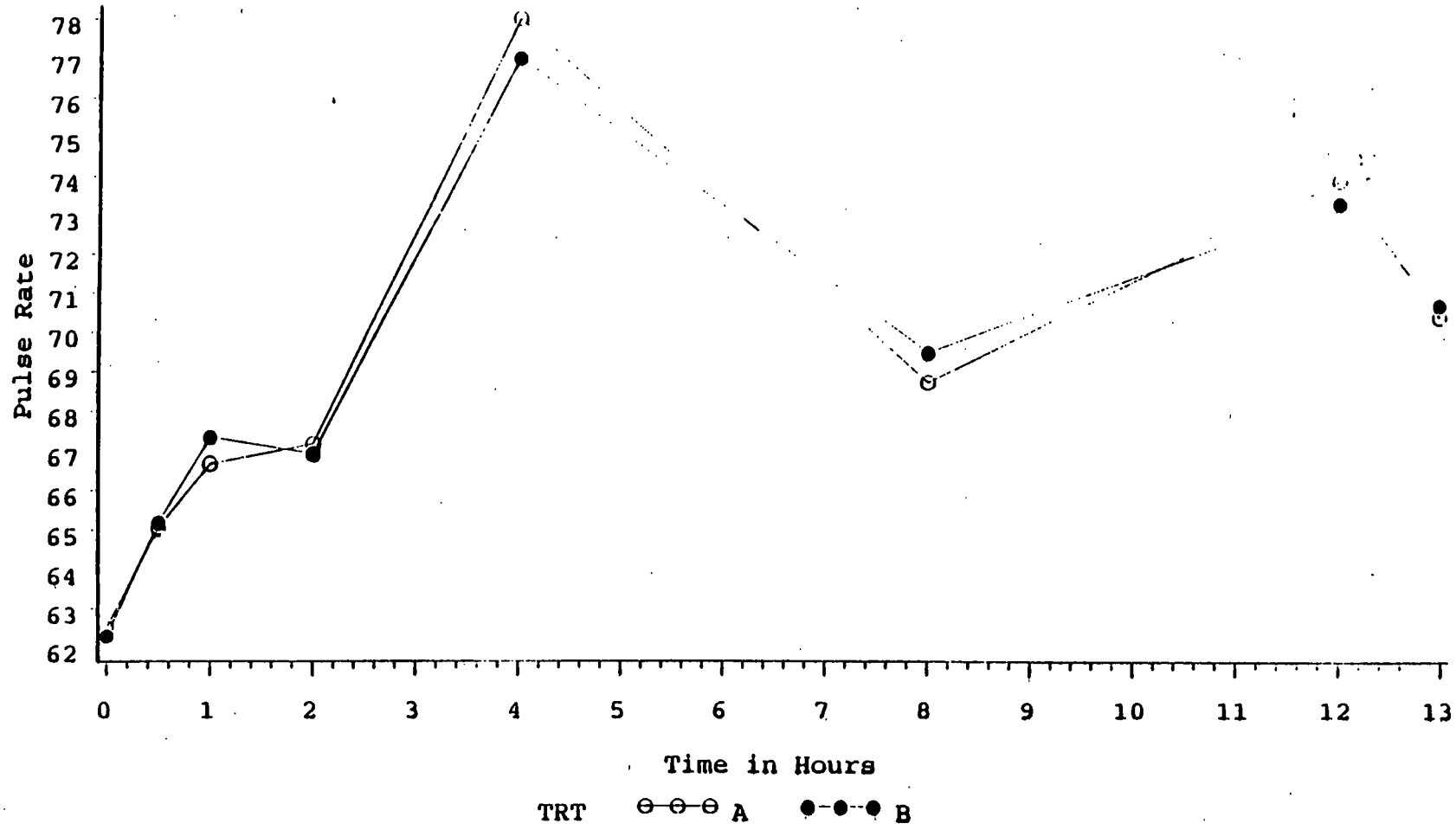
Nitroglycerin (Protocol No. Herc9701)
Mean Blood Pressure Profiles



MEAN AND INDIVIDUAL PULSE RATE PROFILES

Hercon Laboratories, Inc.

Nitroglycerin (Protocol No. Herc9701)
Mean Pulse Rate Profiles



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NOV 24 1995

Nitroglycerin Transdermal System
ANDA #89-885; NTS, 0.4 mg/hr
ANDA #89-884; NTS, 0.2 mg/hr
ANDA #89-886; NTS, 0.6 mg/hr
Reviewer: Sikta Pradhan
WP #89885SDW.D94

Hercon Laboratories, Co.
York, PA
Submission Date:
December 8, 1994

Review of a Bioequivalence Study, Dissolution Data and Waiver Requests

I. INTRODUCTION:

Nitroglycerin is used for the acute relief of angina pectoris. It is used for long term therapy of cardiac insufficiency and cardiac infarction. When given orally, nitroglycerin is extensively metabolized during its first pass, hence alternate routes of administration such as transdermal, are often used. Nitroglycerin transdermal delivery systems are developed in order to control the surface area of application, and the rate of drug delivery, thereby maintaining sustained plasma levels of nitroglycerin over an extended period of time.

This submission is an amendment to the firm's conditionally approved ANDA of Nitroglycerin Transdermal System. The firm has informed the Agency that the product has been reformulated (from a reservior-type to a face adhesive-type transdermal system) and new manufacturing equipment with different/update controls was used in producing the test product of different formulation. The firm had previously (4/27/93) submitted the results of a bioequivalence study comparing its nitroglycerin transdermal system face adhesive patch 0.4 mg/hr (80 mg NTG/15 cm^2) with Transderm-Nitro^R 0.4 mg/hr and Nitro-Dur 0.4 mg/hr. The study had been found unacceptable by the Division of Bioequivalence. The study provided in this amendment is a two-way crossover bioequivalence study conducted on the 10%-reduced-size (13.5 cm^2) Hercon "face-adhesive" NTS-FA, 0.4 mg/hr patch. The current amendment also contains waiver requests for its 0.2 mg/hr and 0.6 mg/hr products.

Objective:

The objective of this two-way crossover single dose study was to evaluate the bioequivalence of a re-sized (10% reduced) Hercon's Nitroglycerin Transdermal System face adhesive patch (NTS FA) formulation relative to a commercially-available TNG reference patch, Transderm-Nitro^R of Ciba-Geigy.

In-Vivo Study:

The study was conducted in healthy volunteers. The clinical study

was conducted at ( ) under the supervision of ( ) Principal Investigator. The analytical study was conducted at ( ).

Study Dates: April 2, 1994 - May 8, 1994
Study Design:

A randomized 2-way crossover, single dose bioequivalence study including a Hercon nitroglycerin patch formulation and a commercially available nitroglycerin refefence patch manufactured by Ciba Geigy was conducted according to protocol # 567794.

Subjects: Forty (40) healthy male and female volunteers (16 males and 24 females) between 18-54 years of age and within ±15% of their ideal body weight according to Metropolitan Life Insurance Company Bulletin, 1983, were selected for the study after 1) Physical Examination, 2) Medical and Complete Routine Laboratory Tests (hematology, blood chemistry, urinalysis, etc.) Female subjects tested negative for pregnancy, and were either postmenopausal, surgically sterile, or practiced an acceptable form of birth control (including oral contraceptives) throughout the duration of the study. The subjects were restricted from all medications for two weeks prior to the first drug administration until after the study was completed. The volunteers were not allowed to drink alcoholic beverages for 48 hours before dosing and throughout the period of sample collection.

Treatments:

A. 1 NTS-FA (Nitroglycerin Transdermal System "face-adhesive" of Hercon) patch (13.5 cm^2) of 72 mg (0.4 mg/hr) dose, applied for 24 hours; Lot # M0504NG/556; Potency: 97.0%, Lot size: ---- patches **Not provided.**

B. 1 Transderm-Nitro^R (Ciba Geigy) patch (20 cm^2) of 50 mg (0.4 mg/hr) dose, applied for 24 hours; Lot # C5340; Potency: 99.0%, **Expiry date:**--------Not provided.

Dose Administration: Each subject received two (2) treatments during the study with a 1-week washout period between them.

Drug Washout Period: One week

Site of Patch Application: The skin at the site of application was clean and dry. Each patch was applied to the chest of each subject approximately halfway between the nipple and medio-clavicular line for 24 hours. The patch including the protective linear was weighed in an analytical balance prior to the application. The protective liner was removed and the patch was applied, and the protective liner was re-weighed. The liner was then transferred into a protective pouch and the pouch was sealed

by folding the top over and securing with tape.

Vital signs: Vital signs such as, heart rate, blood-pressure, respiratory rate, etc. were determined periodically during the study. Times of measurement were: 0 (pre-dose), 0.5, 1, and 6 hours after application of each TNG-patch, and immediately after removal of each patch (24 hours post-dose). All vital sign measurements were taken within 10 minutes before or after the respective blood sampling.

Meal and Food Restrictions: All volunteers fasted for 8 hours prior to and 1 hours after drug administration. Fluids were restricted within one hour of dosing. Standard meal was served. No caffeine-containing food or beverage was served during the study.

Patch Removal:

The patch was removed within 5 minutes after collection of the 24-hour blood sample. Immediately after patch removed, the subject's skin was visually examined and rated for irritation. The patch from each individual subject was transferred into a protective pouch that was properly identified and sealed. Sealed pouches were sent to the sponsor for analysis of residual nitroglycerin content. However, no data on residual contents of nitroglycerin in the used patches were included in the submission.

Blood Sample Collection:

Venous blood samples (5 ml) were collected prior to (0 time) and at 0.5, 1.0, 1.5, 2, 4, 6, 8, 10, 12, 14, 20, 24 hours after patch application. Blood samples were also collected at 24.25, 24.5, 25, and 26 hours after patch removal. Plasma was separated and kept frozen at -70^{0}C until analysis.

Assay Methodology:

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Assy methodology

Stability:

Stability was examined by quantitation of quality control samples:

1. Frozen control samples were found to be stable through three freeze/thaw cycles for TNG, 1,2-DNG and 1,3-DNG. The test samples were compared with freshly thawed (once only) samples.

The mean value (n=3) for each level of the quality control has a percent difference from theoretical within ±15% for TNG, 1,2-DNG and 1,3-DNG for all of the freeze/thaw cycles.

2. Frozen control samples were stable for at least eighteen weeks at -70°C.

3. TNG, when stored at 0-4°C for 24 hours, was reduced by 24% in concentration at its LOQ level.

Results:

Forty (40) volunteers (16 males and 24 females) were enrolled in the study. Four subjects withdrew from the study prematurely, and the study was completed by thirty-six (36) subjects. The ANOVA analysis was conducted on 36 subjects. Subjects #123 and 127 voluntarily withdrew from the study after completing Period I and Subjects 126 and 140 withdrew from the study because of an adverse events such as headache, nausea and vomiting. There were no serious adverse events during this study. The adverse events experienced by some subjects have been reported in Table 1 (attached). Mean plasma TNG, 1,2-DNG and 1,3-DNG levels are presented in Tables 2, 3, and 4, respectively. The mean pharmacokinetic parameters derived from the plasma data are presented in Tables 5-7.

Statistics: There were two Groups and two Periods. The dosing of Group 2 in Period 1 was started (4/30/94) a week after the dosing of Group 1 in Period 2 (4/23/94). The firm has indicated that there were no significant Group effects observed for TNG, 1,2-DNG and 1,3-DNG pharmacokinetic parameters, and therefore, the Group term was deleted from the ANOVA model, and the analyses were rerun using the model: ANOVA Model Response = Sequence + Subject (Sequence) + Period + Treatment + Error.

Comparison of Test and Reference :

For TNG, the differences between the test and reference products in AUC_{0-T}, AUC_{0-14}, AUC_{0-24} and C_{MAX} were 6% or less and the difference in AUC_{0-inf} was 12%. The 90% confidence intervals (90% CI) for $LnAUC_{0-T}$, $LnAUC_{0-14}$, $LnAUC_{0-24}$ and LnC_{MAX} of the test product were within the acceptable range of 80-125% (see Table 5). But the 90% confidence interval (90% CI) for $LnAUC_{0-inf}$ was outside the 80-125% limit.

For 1,2-DNG, the differences in AUC_{0-T}, AUC_{0-14}, AUC_{0-24}, AUC_{0-inf} and C_{MAX} were 5%. or less. The 90% CI for $LnAUC_{0-T}$, $LnAUC_{0-14}$, $LnAUC_{0-14}$ $LnAUC_{0-inf}$ and LnC_{MAX} of the test product were within the acceptable range of 80-125% (see Table 6).

For 1,3-DNG, these differences were 14% or less and the 90%

confidence intervals for $LnAUC_{0-T}$, $LnAUC_{0-14}$, $LnAUC_{0-24}$ of the test product were outside the acceptable range of 80-125% (see Table 7). The 90% CI for $LnAUC_{0-inf}$ and LnC_{MAX} of the test product were within the acceptable range of 80-125% (see Tables 7).

Table 2
Mean Plasma TNG Levels (pg/mL)

Time (hour)	TEST (A) NST-FA (13.5 cm^2) of Hercon Lot #M0504NG/556 N = 36	Reference (B) Transderm-Nitro® Lot #C5340 (Ciba Geigy) N = 36	Signif. Diff. at p=0.05
Pre-dose	0	0	NS
0.5	56.38 (152*)	89.35 (93)	NS
1.0	105.46 (92)	128.54 (76)	NS
1.5	101.96 (112)	129.14 (72)	NS
2.0	121.36 (83)	170.42 (76)	S
4.0	191.64 (80)	203.87 (88)	NS
6.0	246.75 (72)	238.36 (84)	NS
8.0	194.58 (65)	234.98 (80)	NS
10.0	196.22 (86)	198.92 (76)	NS
12.0	220.12 (80)	200.85 (68)	NS
14.0	191.90 (69)	215.80 (83)	NS
20.0	257.74 (83)	229.83 (84)	NS
24.0	233.59 (74)	222.19 (80)	NS
24.25	94.74 (57)	113.60 (94)	NS
24.50	42.43 (105)	38.01 (81)	NS
25.0	11.79 (99)	8.53 (111)	NS
26.0	1.84 (378)	1.42 (290)	NS

* Coefficient of Variation
N = Total Number of Subjects

Table 3
Mean Plasma 1,2-DNG Levels (ng/mL)

Time (hour)	TEST (A) NST-FA (13.5 cm^2) of Hercon Lot #M0504NG/556 N = 36	Reference (B) Transderm-Nitro® Lot #C5340 (Ciba Geigy) N = 36	Signif. Diff. at p=0.05
Pre-dose	0	0	
0.5	0.26 (199*)	0.42 (103)	S
1.0	1.05 (109)	1.42 (72)	S
1.5	1.70 (96)	2.13 (64)	S
2.0	1.94 (87)	2.52 (60)	S
4.0	2.81 (67)	3.20 (53)	S
6.0	3.14 (62)	3.38 (50)	NS
8.0	3.50 (66)	3.66 (47)	NS
10.0	3.38 (64)	3.49 (45)	NS
12.0	3.23 (64)	3.41 (45)	NS
14.0	3.24 (63)	3.30 (45)	NS
20.0	3.31 (57)	3.56 (45)	NS
24.0	3.20 (56)	3.63 (43)	S
24.25	3.08 (51)	3.50 (38)	S
24.50	2.37 (53)	2.59 (41)	NS
25.0	1.38 (52)	1.49 (39)	NS
26.0	0.67 (57)	0.68 (48)	NS

* Coefficient of Variation
N = Total Number of Subjects

Table 4
Mean Plasma 1,3-DNG Levels (ng/mL)

Time (hour)	TEST (A) NST-FA (13.5 cm^2) of Hercon Lot #M0504NG/556 N = 36	Reference (B) Transderm-Nitro® Lot #C5340 (Ciba Geigy) N = 36	Signif. Diff. at p=0.05
Pre-dose	0	0	0
0.5	0.02 (338*)	0.04 (181)	--
1.0	0.13 (136)	0.23 (75)	S
1.5	0.25 (89)	0.36 (55)	--
2.0	0.31 (72)	0.44 (52)	S
4.0	0.42 (59)	0.51 (44)	S
6.0	0.48 (56)	0.54 (43)	S
8.0	0.50 (58)	0.56 (41)	NS
10.0	0.51 (57)	0.56 (41)	NS
12.0	0.50 (57)	0.55 (41)	NS
14.0	0.49 (59)	0.53 (40)	NS
20.0	0.51 (57)	0.57 (43)	S
24.0	0.48 (55)	0.56 (41)	S
24.24	0.46 (50)	0.55 (36)	S
24.50	0.38 (52)	0.44 (38)	S
25.0	0.26 (50)	0.30 (36)	S
26.0	0.12 (83)	0.15 (55)	S

* Coefficient of Variation
N = Total Number of Subjects

Table 6
Mean Pharmacokinetic Parameters for Plasma TNG

Parameters	Test(A) NST-FA (13.5 cm^2) of Hercon Lot #M0504NG/556 N=36	Reference(B) Transderm - Nitro® Lot #C5340 (Ciba Geigy) N=36	Ratio A/B x100	90% C.I. Based on LSM. Subj. = 36
AUC_{0-T}(pg.hr/mL)	4977 (62)*	5067 (68)	99.3	83; 115
$LnAUC_{0-T}$	7.6596 (8)	7.7408 (8)	92.6	81; 105
Geometric mean	2120.91	2300.31		
AUC_{0-14}(pg.hr/mL)	2574 (63)	2755 (65)	94.1	80; 108
$LnAUC_{0-14}$	8.3000 (8)	8.3215 (7)	98.6	87; 112
Geometric mean	4023.87	4111.32		
AUC_{0-24} (pg.hr/mL)	4906 (62)	4996 (68)	99.2	83; 115
$LnAUC_{0-24}$	8.3155 (8)	8.3361 (7)	98.7	87; 112
Geometric mean	4086.73	4171.79		
AUC_{0-Inf}(pg.hr/mL)	6397 (48)	6769 (56)	85.2	59;112
$LnAUC_{0-Inf}$	8.6397 (6)	8.6874 (6)	88.4	72; 108
Geometric mean	5651.63 (N=22)	5927.75 (N=18)		
C_{MAX} (pg/mL)	376 (61)	353 (63)	108	93; 123
LnC_{MAX}	5.7422 (11)	5.6846 (11)	107	93; 123
Geometric mean	311.75	294.3	105.9	
T_{max} (hour)	12.36 (63)	11.03 (63)	111	
t1/2 (hour)	0.413 (73)	0.373 (51)	106	
KE (1/hour)	2.187 (40)	2.358 (47)	94.2	

( )* Coefficient of Variation
N = Total Number of Subjects

Table 6

Mean Pharmacokinetic Parameters for Plasma 1,2-DNG

Parameters	Test(A) NST-FA (13.5 cm^2) of Heroon Lot #M0504NG/556 N=36	Reference(B) Transderm -Nitro® Lot #C5340 (Ciba Geigy) N=36	Ratio A/B x100	90% C.I. Based on LSM. Subj.=36
AUC_{0-T}(ng.hr/mL)	75.3 (62)*	81.4 (45)	92.9	85; 101
$LnAUC_{0-T}$	3.5089 (16)	3.6416 (13)	88.0	82; 94
Geometric mean	33.41	38.15		
AUC_{0-14}(ng.hr/mL)	39.3 (67)	42.7 (48)	92.3	83; 101
$LnAUC_{0-14}$	4.1253 (13)	4.2500 (11)	88.7	83; 95
Geometric mean	61.89	70.10		
AUC_{0-24} (ng.hr/mL)	71.9 (63)	77.6 (46)	93	85; 101
$LnAUC_{0-36}$	4.1736 (13)	4.2988 (11)	88.6	83; 95
Geometric mean	64.95	73.61		
AUC_{0-Inf}(ng.hr/mL)	76.2 (62)	82.2 (45)	93.1	85; 101
$LnAUC_{0-Inf}$	4.1851 (13)	4.3083 (11)	88.8	83; 95
Geometric mean	65.70	74.31		
C_{MAX} (ng/mL)	3.78 (59)	4.00 (42)	94.9	86; 104
LnC_{MAX}	1.2022 (41)	1.2994 (33)	91.1	85; 97
Geometric mean	3.327	3.667		
T_{max} (hour)	15.5 (47)	16.1 (45)	95.7	
t1/2 (hour)	0.8083 (20)	0.7492 (16)	108	
KE (1/hour)	0.8878 (19)	0.9476 (15)	93.3	

( )* Coefficient of Variation
N = Total Number of Subjects

Table 7

Mean Pharmacokinetic Parameters for Plasma 1,3-DNG

Parameters	Test(A) NST-FA (13.5 cm^2) of Heroon Lot #M0504NG/556 N=36	Reference(B) Transderm -Nitro® Lot #C5340 (Ciba Geigy) N=36	Ratio A/B x100 Based on LSM	90% C.I. Based on LSM. Subj.=36
AUC_{0-T}(ng.hr/mL)	11.4 (58)*	13.06 (41)	88.0	81; 94
$LnAUC_{0-T}$	1.6430 (30)	1.8402 (23)	82.5	77; 88
Geometric mean	5.171	6.298		
AUC_{0-14}(ng.hr/mL)	5.88 (59)	6.85 (42)	86.3	79; 94
$LnAUC_{0-14}$	2.2516 (23)	2.4370 (17)	83.6	78; 90
Geometric mean	9.503	11.44		
AUC_{0-24} (ng.hr/mL)	10.9 (58)	12.39 (42)	88.2	82; 95
$LnAUC_{0-24}$	2.2996 (23)	2.4891 (16)	83.2	78; 89
Geometric mean	9.97	12.05		
AUC_{0-Inf}(ng.hr/mL)	12.0 (55)	13.31 (41)	88.6	82; 95
$LnAUC_{0-Inf}$	2.3717 (19)	2.5102	85.6	81; 91
Geometric mean	10.71 (N=35)	12.31		
C_{MAX} (ng/mL)	0.561 (52)	0.629 (38)	89.6	84; 96
LnC_{MAX}	-0.6795	-0.5316	88.7	82; 91
Geometric mean	0.5069	0.5877		
T_{max} (hour)	15.8 (43)	15.02 (46)	106	
t1/2 (hour)	1.09 (25)	1.023 (24)	106	
KE (1/hour)	0.670 (23)	0.715 (24)	94.7	

( )* Coefficient of Variation
N = Total Number of Subjects

The dissolution (drug release) testing data are presented in Table 8 below:

Table 8. In Vitro Dissolution Testing (drug release)

Drug: NTS-FA Transdermal System
Dose Strengths: 0.4 mg/hr; Label Claim: 72 mg/13.5 cm. sq.
ANDA No.: 89-885
Firm: Hercon Lab.
Submission Date: December 8, 1994

I. Conditions for Dissolution Testing:

USP XXII Paddle (*Apparatus 5) RPM: 50
No. Units Tested: 12
Medium: Water; Volume: 500 mL
Specifications: See in Table 9 below
Reference Drug: Transderm-Nitro® (0.4 mg/hr); Label Claim: 50 mg/20 cm. sq.
Assay Methodology:

*The test units were mounted to stainless steel blocks and placed in the dissolution medium.

II. Results of In Vitro Dissolution Testing:

Sampling Times (Hour)	Test Product:Patch Lot # M0504NG/556 Strength 0.4 mg/hr; 72 mg/13.5 cm^2			Reference Product: Patch Lot # C5340 Strength 0.4 mg/hr ; 50 mg/20 cm^2		
	Mean %	Range	%CV	Mean %	Range	%CV
0.5	60.1		1.0	4.5		3.7
1	78.9		0.7	5.9		3.7
1.5	85.2		0.9	7.2		4.1
2	87.7		1.0	8.4		3.9
4	90.1		0.8	13.0		5.0
6	90.1		1.0	17.4		5.7
8	89.7		2.7	21.8		5.8
10	90.0		1.4	25.8		5.9
12	90.5		1.1	29.9		6.1
14	90.6		1.9	35.6		9.6
20	91.2		1.6	45.8		5.7
24	91.2		2.6	53.0		5.7

Comparative Dissolution- Patch Size Proportionality has been presented in Table 9 (attached).

Formulations:

The compositions of three proposed strengths of Hercon's Nitroglycerin Transdermal System are presented below:

Components	Strengths 0.2 mg/hr	0.4 mg/hr	0.6 mg/hr
Patch size	6.75 cm^2	13.5 cm^2	20.2 cm^2
Nitroglycerin	36.0 mg	72.0 mg	108.0 mg
Adhesive Polymer	12.6 mg	25.3 mg	37.9 mg
Adhesive Polymer	15.4 mg	30.9 mg	46.3 mg
Backing Film	6.750 cm^2	13.5 cm^2	20.25 cm^2
Coated Reservoir Weight	64.1 mg	128 mg	192.71 mg

Comments:

1. For nitroglycerin (TNG) of test product, the 90% confidence interval for $LnAUC_{0-T}$, $LnAUC_{0-14}$, $LnAUC_{0-24}$, and LnC_{MAX} were within the 80% to 125% limit. However, the 90% confidence intervals for $LnAUC_{0-inf}$ remained outside the 80-125% limit.

2. For 1,2-dinitroglycerin of test product, the 90% confidence intervals (CI) for $LnAUC_{0-T}$, $LnAUC_{0-14}$, $LnAUC_{0-24}$, $LnAUC_{0-inf}$ and LnC_{MAX} were within the acceptable range of 80-125%. However, for 1,3-dinitroglycerin of test product, the 90% confidence intervals (CI) for $LnAUC_{0-T}$, $LnAUC_{0-14}$ and $LnAUC_{0-24}$ were outside the acceptable range of 80-125%.

3. The dosing of Group 2 in Period 1 was started (4/30/94) a week after the dosing of Group 1 in Period 2 (4/23/94). In order to establish the fact that the difference between the products are not significant in both groups, the firm should be advised to conduct the analysis using the following statistical model:

Model Y = Seq Group Seq*Group Subj(Seq Group) Per(Group) Trt Trt*Group.

If Trt*Group is not significant (p> 0.10), Trt*Group could be dropped from the model. Then the following model could be used:

Model Y = Seq Group Seq*Group Subj(Seq Group) Per(Group) Trt;

or, Model Y = Seq Subj(Seq) Per(Group) Trt.

In either case, the period effect should be modeled as Per(Group), and not just Per. It would be to the benefit of the firm to try these analyses, since their own analysis did not meet the 90% C.I. criterion.

4. The firm has conducted the in vivo bio-study in 36 subjects, but has reported "40 subjects" in all headings of Tables and Figures.

5. The firm has determined the residual content of nitroglycerin in the used patches. However, the data were not included in the submission.

6. The dissolution (drug release) testing conducted by Hercon Laboratories on its Nitroglycerin Transdermal System Face Adhesive Patch, 0.4 mg/ml, Lot #M0504NG/556 comparing it to Transderm-Nitro®, 0.4 mg/hr, Lot #C5340 manufactured by Ciba-Geigy is incomplete. The first time point in the release rate data submitted to the Agency is a 30-minute time point, however, firm's proposed drug release specifications contain a 15-minute time point. The firm should be advised to establish the appropriate specifications for the release rate of its test product from the data obtained in the drug release study.

7. The drug release data were derived from 6 dosage units of 0.2 mg/hr and 0.6 mg/hr patches. The firm should de advised that in vitro dissolution (drug release) testing should be conducted on 12 individual units of the test and reference products and the summary report should include the raw, mean, range and coefficient of variation data.

Recommendations:

1. The in vivo bioequivalence study conducted by Hercon Laboratories on its Nitroglycerin Transdermal System Face Adhesive Patch (72 mg /13.5 cm^2) of 0.4 mg/hr, Lot #M0504NG/556 comparing it to Transderm-Nitro® patch (50 mg /20 cm^2) of 0.4 mg/hr, Lot #C5340 manufactured by Ciba Geigy is incomplete for reasons cited in comments #1-7 above.

2. The dissolution (drug release) testing conducted by Hercon Laboratories on its Nitroglycerin Transdermal System Face Adhesive Patch (13.5 cm^2), 0.4 mg/ml, Lot #M0504NG/556, comparing it to Transderm-Nitro® (Ciba Geigy), 0.4 mg/hr, Lot #C5340 is incomplete due to the reason cited in comment #7 above.

3. The drug release testing conducted on 0.2 mg/hr and 0.6 mh/hr patches is not acceptable for reasons cited in comments #6 & #7 above.

4. The request for waiver of in vivo testing will not be considered until an acceptable in vivo bioequivalence study is conducted by the firm on this drug product.

5. The firm should be advised of the Comments (#1 - #7) and Recommendations, above.

/S/

Sikta Pradhan, Ph. D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHUANG
FT INITIALED YCHUANG /S/ 11/22/95

Concur: /S/ Date: 11/24/95
Keith K. Chan, Ph. D.
Director, Division of Bioequivalence

cc: ANDA # 89-885 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-344 (CViswanathan), HFD-652 (Huang, Pradhan), Drug File, Division File.

SP/06-16-95/X:\wpfile\Pradhan\89885SDW.D94

Table 1
Summary and Frequency of Adverse Events For Each Treatment

Adverse Event	NTS FA-13.5 No. of Events	Transderm-Nitro No. of Events
Headache	33	33
Nausea	7	8
Vasovagal Episode	1	5
Vomiting	2	2
Dizziness	1	1
Itching at Patch Site	2	-
Sore Throat	-	1
Tiredness	-	2
Lightheadedness	1	-
Nosebleed	1	-
Stinging Sensation at Patch Site	1	-
Anxiety	-	1
Dyspepsia	-	1
Throat Abrasion	-	1
Warm Sensation	-	1

Table 9

NITROGLYCERIN TRANSDERMAL FACE ADHESIVE PRODUCT (NTS–FA)

COMPARATIVE DISSOLUTION– PATCH SIZE PROPORTIONALITY

Patch Size (sq. cm.)	Nitroglycerin Content (mg)	Lot # Tested	Nitroglycerin released (mg) (average of 6 units) 15 min.	30 min.	60 min.	Nitroglycerin released (% label claim) (average of 6 units) 15 min.	30 min.	60 min.
6.75	36	L0974NG/560	14.1	22.7	29.8	39.2	63.1	82.8
13.5	72	M0504NG/556	27.8	44.6	58.0	38.6	61.9	80.6
20.25	108	L0974NG/561	43.0	69.0	89.7	39.8	63.9	83.1

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Dissolution Specifications: 15 min: % of label claim
30 min: % of label claim
60 min: % of label claim

[redacted]

FIGURE I

COMPARATIVE DISSOLUTION PROFILES OF HERCON NTS-FA VERSUS TRANSDERM-NITRO

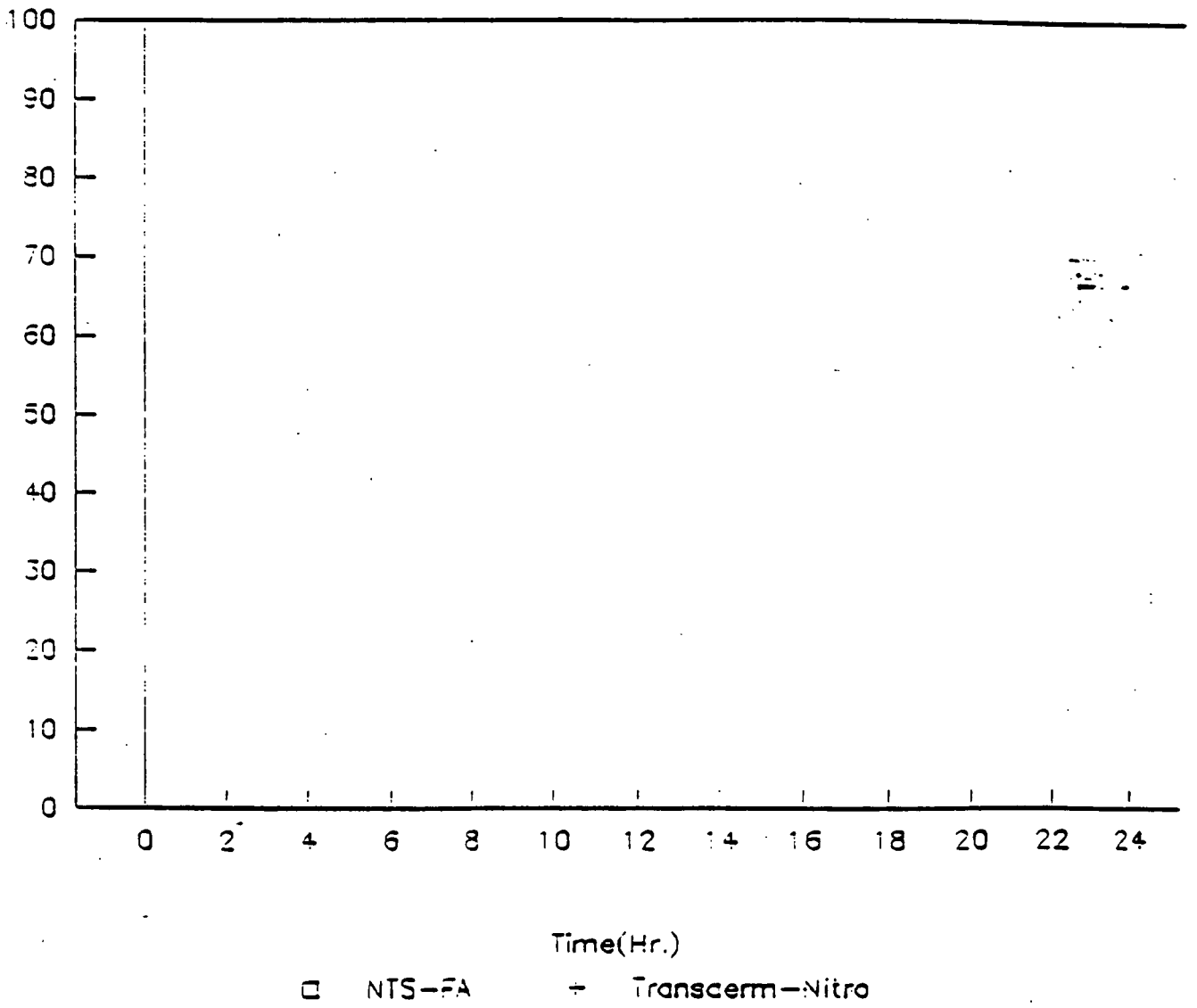
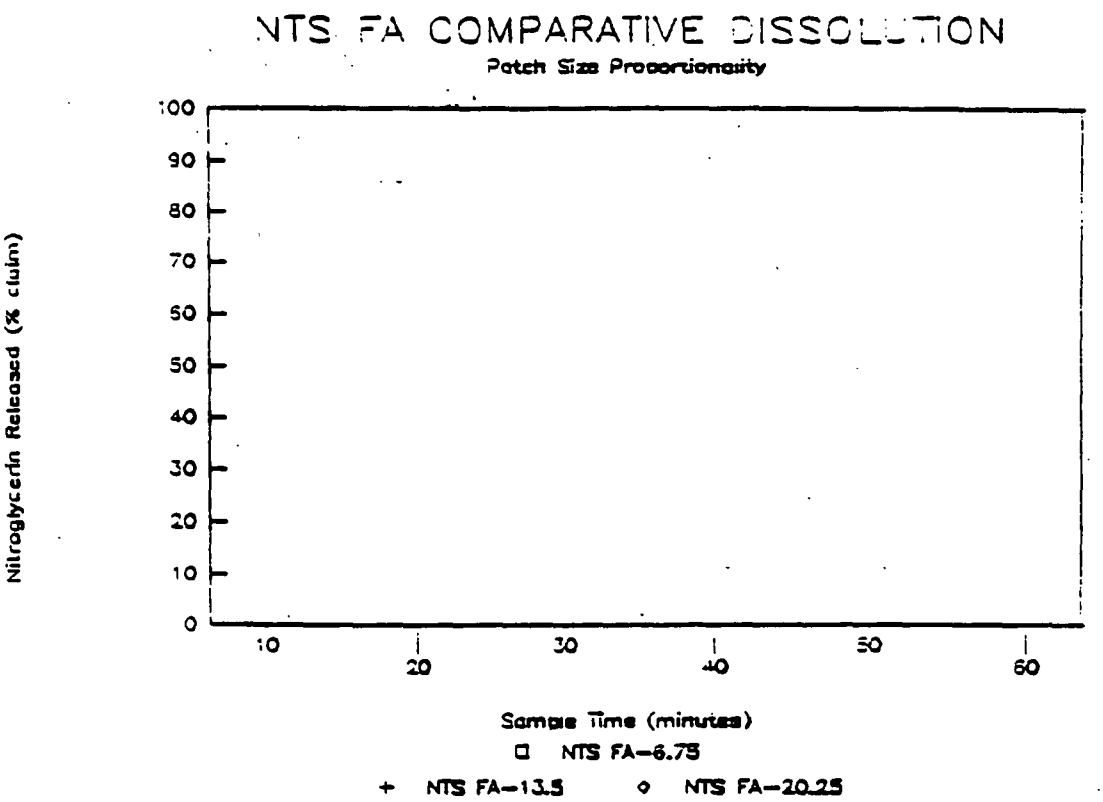


Fig. 2.


NTS FA COMPARATIVE DISSOLUTION
Patch Size Proportionality
Nitroglycerin Released (% claim)
100
90
80
70
60
50
40
30
20
10
0
10
20
30
40
50
60
Sample Time (minutes)
NTS FA-6.75
NTS FA-13.5
NTS FA-20.25

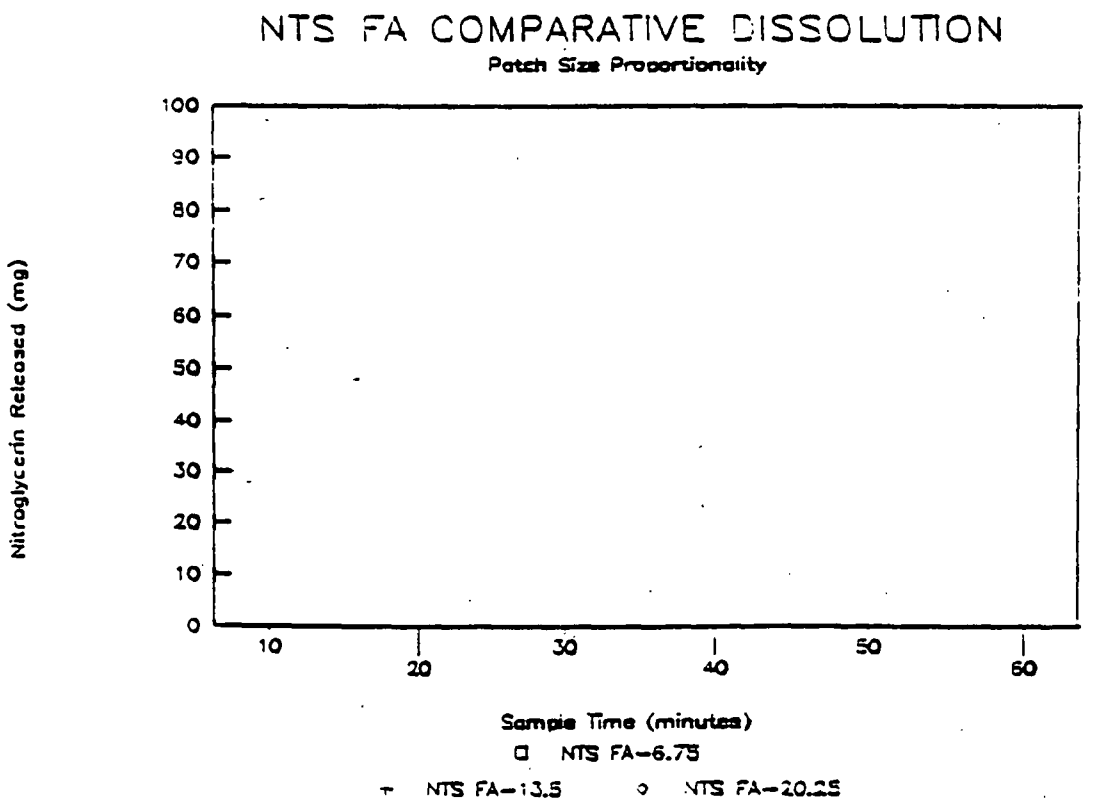

NTS FA COMPARATIVE DISSOLUTION
Patch Size Proportionality
Nitroglycerin Released (mg)
100
90
80
70
60
50
40
30
20
10
0
10
20
30
40
50
60
Sample Time (minutes)
NTS FA-6.75
NTS FA-13.5
NTS FA-20.25

FIGURE # 3

HERCON LABORATORIES CORPORATION
BIOEQUIVALENCE EVALUATION OF TWO NITROGLYCERIN PATCHES IN 40 HEALTHY VOLUNTEERS
TRINITROGLYCERIN ANALYSIS: MEAN (+/− SD) PLASMA CONCENTRATION VS. TIME

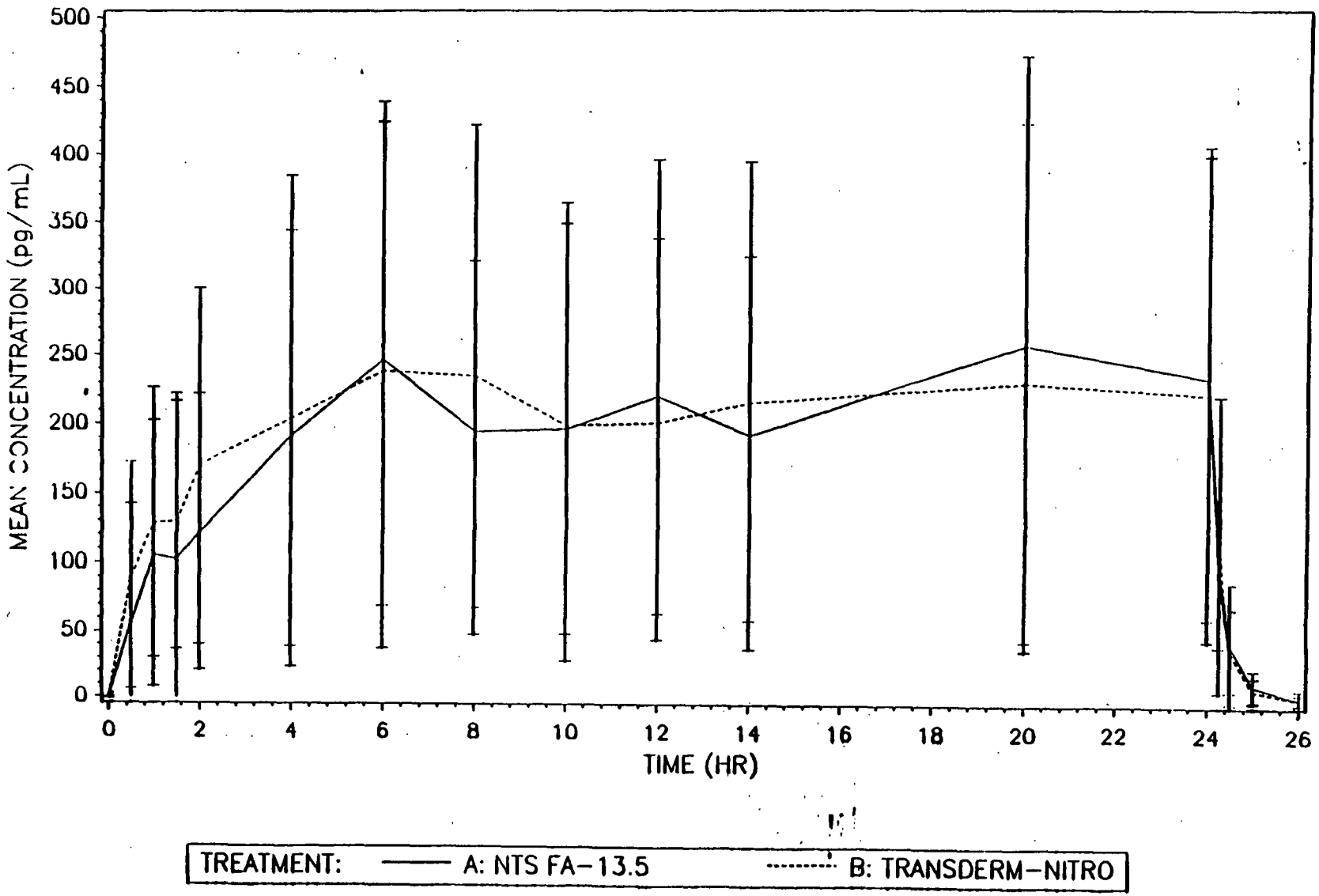


FIGURE 4

HERCON LABORATORIES CORPORATION

BIOEQUIVALENCE EVALUATION OF TWO NITROGLYCERIN PATCHES IN 40 HEALTHY VOLUNTEERS

1,2-DINITROGLYCERIN ANALYSIS: MEAN (+/- SD) PLASMA CONCENTRATION VS. TIME

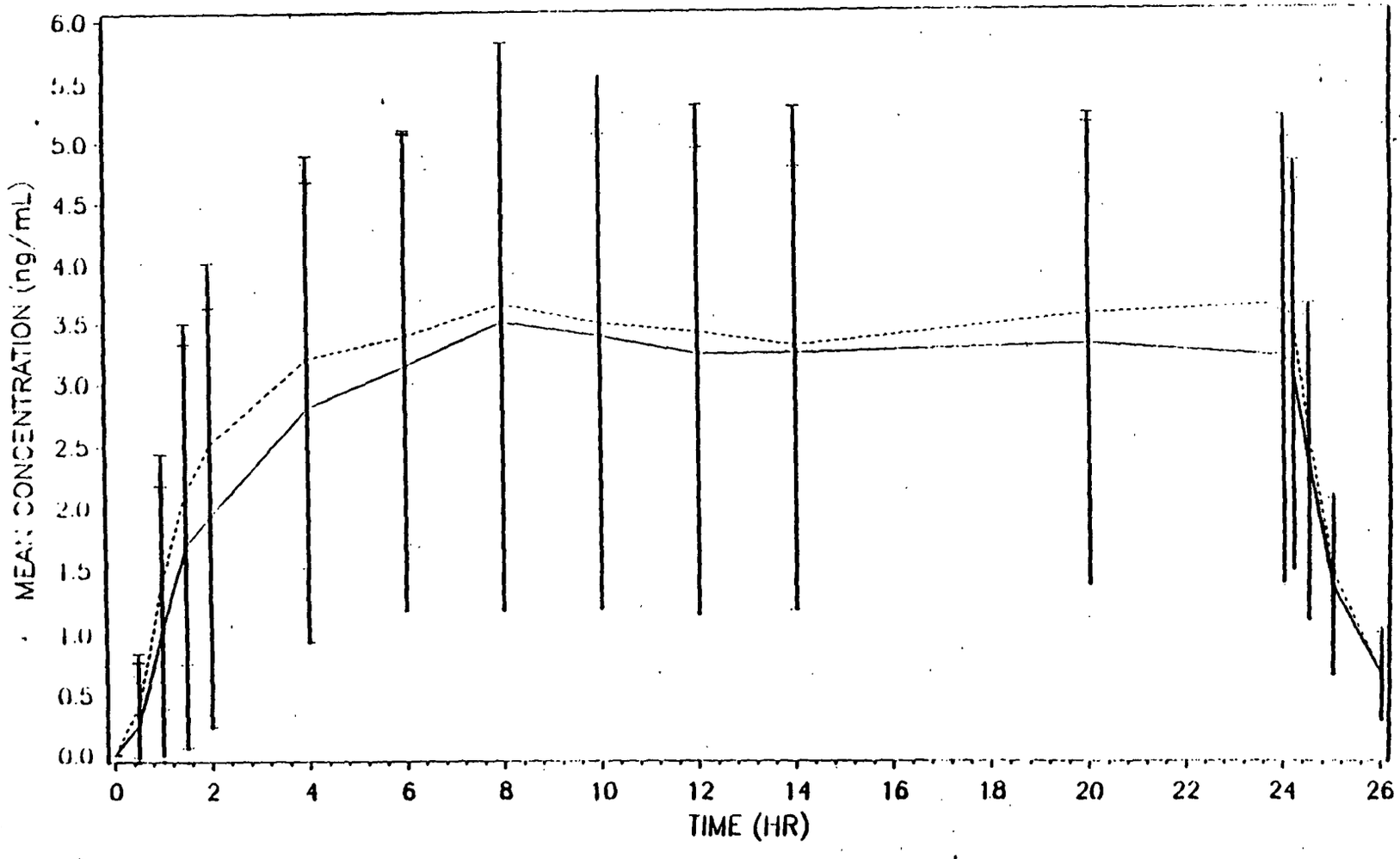


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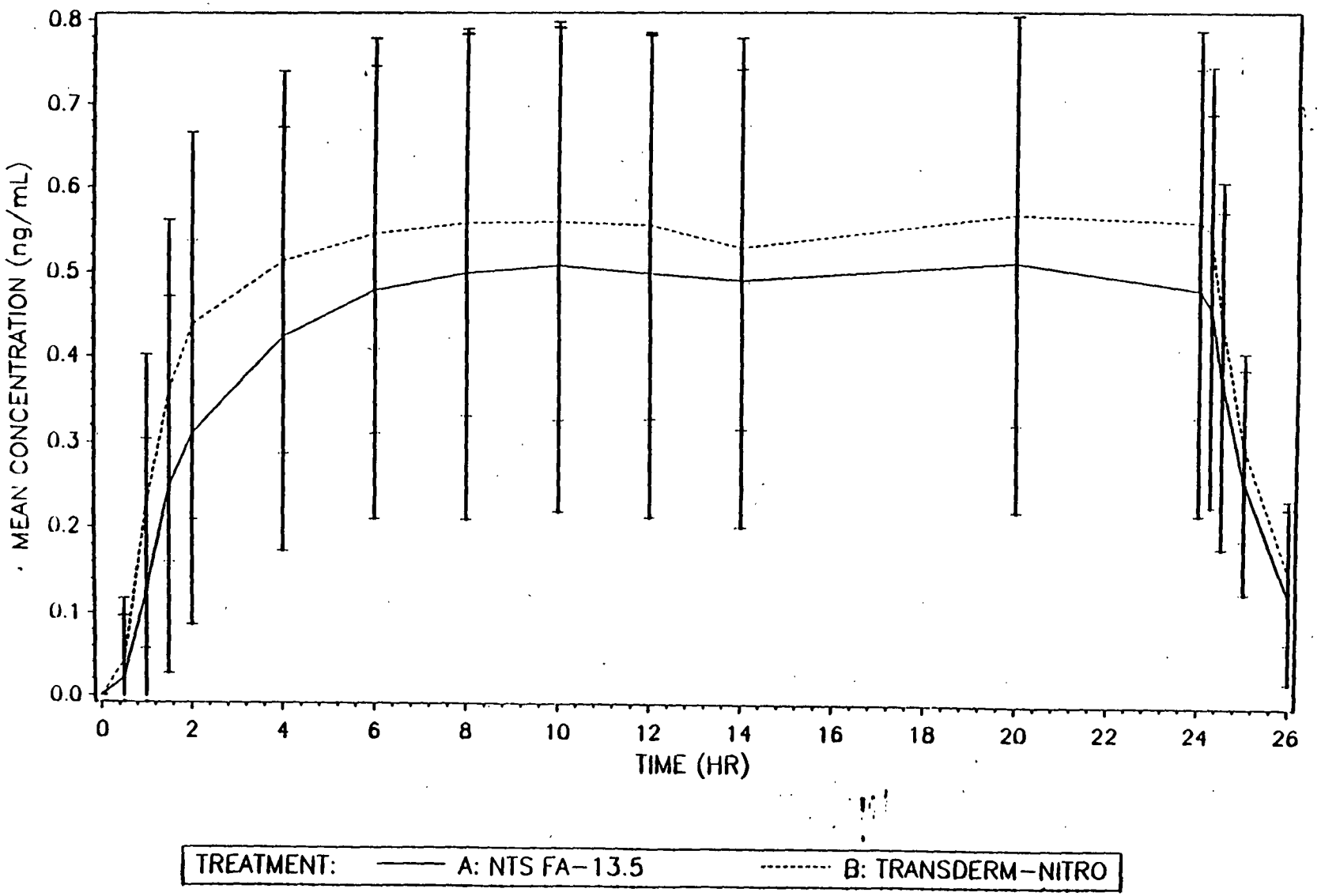
FIGURE 5

HERCON LABORATORIES CORPORATION
BIOEQUIVALENCE EVALUATION OF TWO NITROGLYCERIN PATCHES IN 40 HEALTHY VOLUNTEERS
1,3-DINITROGLYCERIN ANALYSIS: MEAN (+/- SD) PLASMA CONCENTRATION VS. TIME



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Nitroglycerin Transdermal System
0.2 mg/hr, 0.4 mg/hr, 0.6 mg/hr
ANDA #89-884, 89-885, 89-886
Reviewer: YC Huang
89885S.493

Hercon Laboratories
York, PA
Submission date:
April 27, 1993

Review of A Bioequivalence Study
(a repeated insult patch test and waiver request)

Introduction The submission is an amendment to the firm's conditionally-approved ANDA of this drug product (December 8, 1987). The firm has stated that the product has been reformulated and that the formulation, methods, and controls differ substantially from those for the previous formulation. The firm has also stated that all materials previously submitted to this application are replaced by this amendment and that all previously submitted information should be disregarded.

The submission contains the results of two *in vivo* studies: (1) Bioequivalence Evaluation of Three Glyceryl Trinitrate patches in 36 Healthy Volunteers, and (2) Adhesive Wear Properties and Repeated Insult Patch Test (RIPT) to Three Transdermal Nitroglycerin Patches. Waiver requests for the 0.2 mg/hr and 0.6 mg/hr strengths of the test product have also been made.

I. Bioequivalence study

Objective

The objective of the bioequivalence study was to compare the bioavailability of nitroglycerin (NTG) and its 1,2- and 1,3-dinitroglycerin metabolites (1,2-DNG and 1,3-DNG) following a new NTG patch with two commercially available NTG patches.

Products tested

Test (A)	Nitroglycerin Transdermal System, containing 80 mg of NTG, delivering NTG at 0.4 mg/hour (10 mg/24 hours), manufactured by Hercon. (Lot #Y0632NG/487). Batch size was not given.
Reference I (B)	Transderm Nitro®, containing 50 mg of NTG, delivering NTG at 0.4 mg/hour (10 mg/24 hours), manufactured by Ciba Geigy. (Lot #1M149250)
Reference II (C)	Nitro-Dur®, containing 80 mg of NTG, delivering NTG at 0.4 mg/hour (10 mg/24 hours), manufactured by Key Pharmaceuticals. (Lot#D2212411)

Study design The study was conducted following a three-treatment, three-period, six-sequence crossover design. The washout period was at least three days.

Sequence	Subject Number
A B C	5, 6, 12, 23, 25, 34
B C A	1, 7, 8, 24, 29, 31
C A B	3, 10, 15, 19, 27, 32
A C B	18, 21, 22, 28, 35, 36
C B A	2, 4, 9, 13, 16, 30
B A C	11, 14, 17, 20, 26, 33

[**Reviewer's Note**: Subjects were divided into three groups.]

The dosing times for each group are as follows:

Group No.	Subject No.	Dosing Time
1	1 - 9 (N=9)	6/18/92, 6/25/92, 7/2/92
2	10, 12-18, 20-22, 24 (N=12)	6/20/92, 6/27/92, 7/4/92
3	11, 19, 23, 25-36 (N=15)	6/23/92, 6/30/92, 7/7/92

Site of patch application Each patch was applied to the subject's chest in the mid-clavicular line over the fifth intercostal space, on either the left or right side of the thorax for 24 hours. The whole patch (i.e., including the protective liner) was weighed using an analytical balance prior to the application and the weight was recorded.

Study sites and investigators

Investigators were:
(Data analysis), and
(Assay)

Subject Selection

1. Pre-study health screening

   The pre-study screening was performed within 14 days prior to the study. The screening consisted of an interview, physical examination, EKG, and laboratory tests, including a urinary drug screen.

2. Pre-Study NTG screening (test-treatment)

   All subjects satisfying health screening criteria underwent an 8-hour clinical test-treatment with one of the study's two reference NTG patches. The purpose of this test was to try to identify and screen out those subjects unable to tolerate NTG treatment. This test-treatment was conducted during the 14-day period between health screening and start of the first formal NTG treatment. No blood samples were taken during this test-treatment.

Forty-three subjects entered the study and seven were dropped during the test-treatment. Of the 36 subjects who received formal treatment, five subjects (#8, #20, #29, #30, and #36) dropped after the first period, one subject (#19) dropped after the second period, and 30 subjects completed all three treatments. The demographics for subjects who received formal treatment were as follows: mean age 30.4 years (range, 18-46 years), mean height 69.8 inches (range, 64.5-76 inches), and mean weight 160.3 pounds (range, 124-223 pounds). The weights were within ±15% of the ideal weight.

Confinement and restriction Subjects were confined in the clinical facility from the evening prior to dosing until after the collection of 26-hour blood sample, for a total of 38 hours. Subjects were abstained from any caffeine-containing foods or beverages for 48 hours prior to each patch application. Subjects were told not to engage in strenuous exercise or lie down flat until at least five hours after patch application.

Blood samples Venous blood samples (8 mL each) were collected at the following times: 0 (pre-dose), 0.5, 1, 1.5, 2, 4, 6, 9, 12, 16, 20, 24, 24.25, 25, and 26 hours after dosing. Blood tubes were placed into an ice-water-bath at 4 degrees C within 5 seconds of blood withdrawals and centrifugation was completed in a cooled centrifuge within 15 minutes of blood withdrawals. Plasma samples were frozen at -70 degrees C until analysis.

Assay

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confidential

commercial

information

ASSAY

Stability: The firm did not submit the stability data of the study samples.

Vital signs Vital signs (heart rate, blood pressure, and respiratory rate) were measured at the following times: 0 (pre-dose), 0.5, 1, 4, and 12 hours after patch application, and immediately after removal of each patch (24 hours post-dose). At each vital sign assessment period, subjects were interviewed to elicit information on possible side effects.

Patch removal The patch was removed within 5 minutes after collection of the 24-hour blood sample. Immediately after patch removal, the subject's skin at the application site was visually examined and assigned a score for irritation. The site of application was wiped twice with an individual alcohol swab. Patch and swab were transferred into separate protective pouches. The used patches were analyzed for the residual NTG contents.

Waiver request To support the waiver request, the firm has submitted the *in vitro* drug release data and formulation information of the test products.

Formulation of the test product

Component	0.2 mg/hr theory qty. per patch	0.4 mg/hr theory qty. per patch	0.6 mg/hr theory qty. per patch
-- Patch size--	7.5 cm^2	15.0 cm^2	22.5 cm^2
Nitroglycerin			
Adhesive Polymer			
Adhesive Polymer			
Coated Reservoir Weight	71.16 mg	142.3 mg	213.5 mg

Drug release study The dissolution (drug release) testing was conducted using the following conditions:

USP Apparatus II (paddle) at 50 rpm
Medium: 500 mL of deionized water at 32° C (± 0.5° C)
Sampling times: 15, 30, and 60 minutes
Analytical method:

The test units were mounted to stainless steel weights and placed in the dissolution medium.

The results were reported as follows: (N = 6)

	Content Claim		In-Vitro release 15 min		30 min		60 min	
	(mg)	mg/hr	mg	%	mg	%	mg	%
Key (Lot #:D2212411)	80	0.4	23.5	29.4	37.4	46.8	52.2	65.2
Ciba (Lot #:1M149250)	50	0.4	1.76	3.52	2.25	4.50	3.02	6.04
Hercon (Lot #:E0692NG/488)	40	0.2	15.6	39.0	26.3	65.8	35.6	89.0
Hercon (Lot #:Y0632NG/487)	80	0.4	33.0	41.2	52.8	66.0	68.7	85.9
Hercon (Lot #:E0762NG/489)	120	0.6	45.4	37.8	73.9	61.6	96.0	80.0

Data analysis The following pharmacokinetic parameters were derived from the plasma concentration-time data:

Cmax and Tmax
Cmin: the lowest concentration during steady-state (where the steady-state interval was determined statistically)
Cav: the average concentration during steady-state
DF (degree of fluctuation): 100% x (Cmax-Cmin)/Cav
AUC(0-24), AUC(0-last), AUC(0-∞): areas under the curve were calculated based on linear and/or log-linear trapezoidal rules.

Results

1. Thirty-six (36) subjects received formal treatment. Five subjects (#8, 20, 29, 30, and 36) dropped after the first period and one subject (#19) dropped after the second period. That is to say 32 subjects received treatment A (Hercon), 33 subjects received treatment B (Transderm-Nitro) and 32 received treatment C (Nitro-Dur). Among them, 30 subjects received both treatments A and B and 31 subjects received both

treatments A and C. The firm reported only 30 sets of data for treatment C, stating that there were no samples between hour 9-24 (5 time points, see page 257) for subject #3 after treatment C.

2. The mean Cp-t profiles and summaries of pharmacokinetic parameters for NTG, 1,2- and 1,3-DNG as reported in the submission (pages 306-308) are shown in Tables 1-3. The corresponding figure is shown in Figure 1 (page 310). The results of Cmax, Cmin, Cav, and DF are summarized in Tables 4-6. The results of 90% confidence intervals are summarized in Tables 7-9.

3. For NTG, the 90% confidence intervals for both Cmax and AUC were outside the acceptable range of 80-125% (for both Hercon versus Transderm-Nitro and Hercon versus Key, see Table 7). The reported Cmax value of Hercon's patch was 27% higher than those of Transderm-Nitro and Nitro-Dur and the AUC(0-24) value of Hercon's patch was 12% and 18% higher than those of Transdermal Nitro and Nitro-dur, respectively Comparison between Hercon's NTG patch and Transderm-Nitro: For 1,2-DNG, the Cmax and AUC(0-24) values of Hercon's patch were 11% and 14% higher than those of Transderm-Nitro, respectively. The 90% confidence intervals for these two parameters were within the range of 80-125%. For 1,3-DNG, the Cmax and AUCs values of Hercon's patch were 2 to 5% higher than those of Transderm-Nitro and the 90% confidence intervals were within the range of 80-125%. Comparison between Hercon's NTG patch and Nitro-Dur: For 1,2-DNG, the Cmax and AUC(0-24) values of Hercon's patch were 15% and 19% higher than those of Nitro-Dur. While the 90% confidence interval for Cmax value is within the range of 80-125%, the value of AUC(0-24) was outside the 80-125% range (i.e., %, Table 8). For 1,3-DNG, the Cmax and AUC values were 8% to 13% higher than those of Nitro-Dur. The 90% confidence intervals for both Cmax and AUC are within the range of 80-125%.

4. The summary of adverse events was reported on page 87 in the submission. The adverse events included headache, nausea, dizziness, lightheadedness and the reactions to the patch site included erythema, stinging/burning, irritation/redness, and itching. The incidences of the adverse events and the reactions to the patch application sites were comparable among the test and the reference products.

Table 1: Mean NTG data

Time (hr)	Hercon Mean	%CV	N	Transderm Nitro Mean	%CV	N	Nitro-Dur Mean	%CV	N
0	0			0			0		
0.5	0.134	125	18	0.117	73	16	0.110	70	20
1.0	0.241	155	25	0.179	128	26	0.130	79	27
1.5	0.224	117	31	0.160	110	30	0.133	73	29
2.0	0.199	101	32	0.176	122	31	0.121	65	30
4.0	0.223	89	32	0.213	69	32	0.180	79	30
6.0	0.249	94	32	0.274	102	32	0.150	74	31
9.0	0.269	90	32	0.264	93	32	0.207	83	31
12.0	0.268	102	32	0.212	99	32	0.193	90	31
16.0	0.239	87	32	0.255	115	32	0.262	82	31
20.0	0.265	92	32	0.286	83	32	0.336	89	30
24.0	0.334	119	32	0.246	122	32	0.198	90	31
24.25	0.168	102	30	0.118	82	32	0.148	65	29
24.50	0.143	164	24	0.0819	80	24	0.073	48	22
25.0	0.102	133	12	0.0539	45	16	0.0537	71	10
26.0	0.131	190	10	0.0442	35	8	0.0639	43	3
Cmax (ng/mL)	0.555	80	31	0.416	81	30	0.417	70	30
AUC(0-24) (hr-ng/mL)	5.96	75	31	5.59	92	30	5.01	69	30
AUC(0-last)	6.11	75	31	5.68	93	30	5.09	68	30
AUC(0-∞)	7.63	70	21	7.33	82	19	6.38	54	21
Tmax (hr)	13.36	60	31	12.94	60	30	16.02	39	30
K (hr^{-1})	1.795	75	21	1.675	79	19	1.957	68	21
T½ (hr)	0.80	138	21	1.43	244	19	0.73	128	21

Table 2: Mean 1,2-DNG data

Time (hr)	Hercon Mean	%CV	N	Transderm Nitro Mean	%CV	N	Nitro-Dur Mean	%CV	N
0	0			0			0		
0.5	0.527	72	10	0.316	60	12	0.339	63	15
1.0	0.949	76	28	0.861	66	31	0.733	55	30
1.5	1.546	70	32	1.334	53	32	1.073	48	32
2.0	2.009	61	32	1.635	47	33	1.346	43	32
4.0	2.695	42	32	2.351	38	33	1.936	42	32
6.0	2.960	40	32	2.592	34	33	2.198	39	32
9.0	3.205	37	32	2.727	33	32	2.530	39	31
12.0	3.180	36	32	2.613	37	32	2.755	42	31
16.0	3.165	35	32	2.607	30	32	2.694	36	31
20.0	3.041	38	32	2.851	31	32	2.925	35	31
24.0	3.333	38	32	2.900	31	32	2.778	34	31
24.25	3.163	34	32	2.736	26	33	2.742	40	31
24.50	2.551	36	32	2.2829	32	33	2.119	40	32
25.0	1.727	37	32	1.3829	36	33	1.358	45	32
26.0	0.878	52	32	0.569	35	33	0.595	54	32
Cmax (ng/mL)	3.732	34	31	3.247	28	30	3.215	35	30
AUC(0-24) (hr-ng/mL)	69.17	37	31	59.13	31	30	57.05	36	30
AUC(0-last)	73.01	37	31	62.21	31	30	60.18	36	30
AUC(0-∞)	75.76	35	30	62.91	31	30	61.02	36	30
Tmax (hr)	18.02	35	31	16.62	42	30	18.53	27	30
K (hr^{-1})	0.708	25	30	0.845	14	30	0.814	20	30
T½ (hr)	1.08	46	30	0.84	15	30	0.88	21	30

Table 3: Mean 1,3-DNG data

Time (hr)	Hercon Mean	Hercon %CV	Hercon N	Transderm Nitro Mean	Transderm Nitro %CV	Transderm Nitro N	Nitro-Dur Mean	Nitro-Dur %CV	Nitro-Dur N
0	0			0			0		
0.5	0.174	51	4	0.151	18	2	0.122	12	4
1.0	0.291	95	17	0.241	59	20	0.247	63	15
1.5	0.312	84	29	0.325	60	29	0.283	57	26
2.0	0.371	59	31	0.413	58	30	0.314	57	31
4.0	0.493	60	32	0.553	50	32	0.440	69	32
6.0	0.555	67	32	0.553	56	33	0.480	61	32
9.0	0.577	72	32	0.571	56	32	0.532	63	31
12.0	0.572	62	32	0.528	57	32	0.579	67	31
16.0	0.610	68	32	0.579	63	32	0.573	77	31
20.0	0.582	72	32	0.587	51	32	0.614	62	31
24.0	0.607	59	32	0.633	60	32	0.560	65	31
24.25	0.573	61	32	0.555	56	33	0.587	61	31
24.50	0.491	64	32	0.507	55	33	0.455	66	32
25.0	0.367	51	32	0.351	59	33	0.3227	62	32
26.0	0.276	68	29	0.214	58	28	0.219	55	23
Cmax (ng/mL)	0.754	56	31	0.728	54	30	0.683	64	30
AUC(0-24) (hr-ng/mL)	12.96	64	31	12.43	56	30	12.10	66	30
AUC(0-last)	13.75	63	31	13.14	56	30	12.79	66	30
AUC(0-∞)	15.01	61	29	13.61	55	30	13.31	64	30
Tmax (hr)	17.21	42	31	16.45	48	30	19.49	26	30
K (hr^{-1})	0.469	47	29	0.570	29	30	0.553	42	30
T½ (hr)	2.22	110	29	1.48	86	30	1.55	61	30

Table 4. The Mean Values of Cmin, Cmax, Cav, and DF for NTG at the Steady State

Parameter	Treatment A Mean (%CV)	Treatment B Mean (%CV)	Treatment C Mean (%CV)
Cmin (9-24), ng/mL	0.135 (107)	0.146 (110)	0.113 (81)
Cmax (9-24), ng/mL	0.504 (82)	0.393 (87)	0.401 (76)
Cav (9-24), ng/mL	0.266 (74)	0.247 (95)	0.246 (73)
DF (9-24), %	129.0 (55)	104.1 (46)	110.7 (50)

Treatment A = Hercon's NTG patch, 0.4 mg/hr
Treatment B = Transderm-Nitro, 0.4 mg/hr
Treatment C = Nitro-Dur, 0.4 mg/hr
For both treatments A and B, N=31. For treatment C, N=30.
The steady state was determined to be between hour 9-24.

Table 5. The Mean Values of Cmin, Cmax, Cav, and DF for 1,2-DNG at the Steady State

Parameter	Treatment A Mean (%CV)	Treatment B Mean (%CV)	Treatment C Mean (%CV)
Cmin (9-24), ng/mL	2.703 (39)	2.285 (30)	2.354 (39)
Cmax (9-24), ng/mL	3.712 (35)	3.148 (31)	3.154 (35)
Cav (9-24), ng/mL	3.170 (35)	2.708 (30)	2.749 (35)
DF (9-24), %	32.5 (69)	32.3 (46)	30.2 (46)

For treatment A, N=31. For both treatments B and C, N=30.
The steady state was determined to be between hour 9-24.

Table 6. The Mean Values of Cmin, Cmax, Cav, and DF for 1,3-DNG at the Steady State

Parameter	Treatment A Mean (%CV)	Treatment B Mean (%CV)	Treatment C Mean (%CV)
Cmin (4-24), ng/mL	0.442 (69)	0.425 (60)	0.409 (74)
Cmax (4-24), ng/mL	0.735 (59)	0.721 (55)	0.668 (65)
Cav (4-24), ng/mL	0.588 (64)	0.559 (56)	0.555 (66)
DF (4-24), %	50.9 (49)	55.9 (67)	48.4 (34)

For treatment A, N=31. For both treatments B and C, N=30.
The steady state was determined to be between hour 4-24.

Table 7. Results of 90% Confidence Intervals of NTG

Parameter	Treatment A	Treatment B	Treatment C	A/B Ratio	A/C Ratio	90% C.I.
LN(Cmax)	-0.869	-1.127	-1.123	1.27	1.27	A/B: 1.06 - 1.52 A/C: 1.06 - 1.52
Geometric mean	0.4195	0.3241	0.3254			
LNAUC(0-24)	1.557	1.431	1.380	1.12	1.18	A/B: 0.97 - 1.30 A/C: 1.01 - 1.37
Geometric mean	4.745	4.183	3.975			
LNAUC(0-last)	1.579	1.446	1.397	1.13	1.18	A/B: 0.97 - 1.31 A/C: 1.02 - 1.37
Geometric mean	4.850	4.246	4.043			
LNAUC(0-∞)	1.820	1.746	1.701	1.12	1.11	A/B: 0.93 - 1.34 A/C: 0.93 - 1.30
Geometric mean	6.1722	5.7355	5.4802			
Tmax (hr)	13.36	12.94	16.02	1.03	0.83	
DF(9-24), %	129.0	104.1	110.7	1.24	1.16	

Calculation of 90% confidence intervals was based on log-transformed data.
Treatment A = Hercon's NTG patch, 0.4 mg/hr
Treatment B = Transderm-Nitro, 0.4 mg/hr
Treatment C = Nitro-Dur, 0.4 mg/hr
The unit for Cmax is ng/mL and for AUC is hr-ng/mL
For treatment A, N= 31 [except AUC(0-∞), N=21].
For treatment B, N= 30 [except AUC(0-∞), N=19].
For treatment C, N= 30 [except AUC(0-∞), N=19].

Table 8. Results of 90% Confidence Intervals of 1,2-DNG

Parameter	Treatment A	Treatment B	Treatment C	A/B Ratio	A/C Ratio	90% C.I.
LN(Cmax)	1.2514	1.1373	1.1049	1.11	1.15	A/B: 1.03 - 1.20 A/C: 1.06 - 1.24
Geometric mean	3.4952	3.1183	3.0189			
LNAUC(0-24)	4.1623	4.0273	3.9780	1.14	1.19	A/B: 1.05 - 1.23 A/C: 1.11 - 1.29
Geometric mean	64.2191	56.1092	53.4101			
LNAUC(0-last)	4.2175	4.0798	4.0318	1.14	1.19	A/B: 1.05 - 1.24 A/C: 1.10 - 1.29
Geometric mean	67.8636	59.1336	56.3622			
LNAUC(0-∞)	4.2585	4.0911	4.0456	1.16	1.20	A/B: 1.06 - 1.26 A/C: 1.11 - 1.31
Geometric mean	70.7038	59.8056	57.1455			
Tmax (hr)	18.02	16.62	18.53	1.08	0.97	
DF(9-24), %	32.5	32.3	30.2	1.01	1.08	

The unit for Cmax is ng/mL and for AUC is hr-ng/mL
For treatment A, N= 31. For treatment B, N= 30.
For treatment C, N= 30.

Table 9. Results of 90% Confidence Intervals of 1,3-DNG

Parameter	Treatment A	Treatment B	Treatment C	A/B Ratio	A/C Ratio	90% C.I.
LN(Cmax)	-0.401	-0.4339	-0.5345	1.02	1.13	A/B: 0.93 - 1.12
Geometric mean	0.6696	0.6480	0.5860			A/C: 1.03 - 1.25
LNAUC(0-24)	2.4240	2.3990	2.3342	1.02	1.08	A/B: 0.93 - 1.12
Geometric mean	11.2909	11.0122	10.3212			A/C: 0.99 - 1.19
LNAUC(0-last)	2.4860	2.4548	2.3903	1.02	1.09	A/B: 0.93 - 1.12
Geometric mean	12.0131	11.6441	10.9168			A/C: 0.99 - 1.19
LNAUC(0-∞)	2.5784	2.4949	2.4356	1.05	1.11	A/B: 0.95 - 1.16
Geometric mean	13.1760	12.1285	11.4227			A/C: 1.01 - 1.23
Tmax (hr)	17.21	16.45	19.49	1.05	0.88	
DF(4-24), %	50.9	55.9	48.4	0.92	1.05	

Treatment A = Hercon's NTG patch, 0.4 mg/hr
Treatment B = Transderm-Nitro, 0.4 mg/hr
Treatment C = Nitro-Dur, 0.4 mg/hr
The unit for Cmax is ng/mL and for AUC is hr-ng/mL
For treatment A, N= 31 [except AUC(0-∞), N=29].
For treatment B, N= 30.
For treatment C, N= 30.

II. Wear and repeated insult patch test

Title Adhesive wear properties and repeated insult patch test (RIPT) of three transdermal nitroglycerin patches

Objectives

To determine and compare the wear characteristics, irritation potential and/or allergic contact sensitization potential of three transdermal adhesive patch test articles (an "active" test article, a placebo control article, and an "active" control article) after repetitive 24-hour applications to the skin of human subjects. The active control article was studied for its wear characteristics only.

Formulations tested

1. Active test article: Hercon's NTS (FA-7.5), 0.2 mg/hr (Lot #E0692NG/488)
2. Placebo control article: Hercon's placebo patch (Lot #61102NBG/496)
3. Active control article: Key's Nitro-Dur®, 0.2 mg/hr (Lot #D1Y04211)

Study site and investigators

Principal investigator:
Medical investigator:

IRB approval The study protocol and the informed consent form were reviewed and approved by the Institutional Review Board at the

Subjects One hundred twenty (120) subjects, 29 males and 91 females, participated in the study. The subjects met the inclusion/exclusion criteria specified in the study protocol and had the ages between 18 and 65 years. The test facility made every effort to enroll subjects who were considered "tolerant" to the major expected side effects of nitroglycerin (i.e., headache, nausea, etc.). Subjects wore the patches under conditions of normal daily activity (work, recreation. shower, bathing, sleeping, etc.). They were instructed not to reaffix any patch should "loosening" be observed, and to note and record the date, time and circumstances under which any of the patches fell off.

Study dates The study was initiated on September 14, 1992 (Subjects #1-104) and September 21, 1992 (Subjects #105-120) and completed on October 23 (Subjects #1-104) and October 30, 1992 (Subjects #105-120).

Study design (induction phase and challenge phase)

Duration of the study The duration of the study was approximately six weeks. Each subject participated in a three-week induction period, followed by a resting period of approximately two weeks. Challenge patch applications were made and scored during the final (6th) week of the study.

Induction phase (Hercon's active and placebo patches): three times a week for three weeks

Twenty-four hour patch applications were made on a Monday, Wednesday, Friday schedule. Twenty-four hour rest periods followed the patch removals on Tuesday and Thursday, and a 48-hour rest period followed the patch removal on Saturday. The application sites were scored by a trained examiner just prior to the next patch application (**Reviewer's note**: From the data presented, it appeared that the firm had also scored the sites right after the removal of the patch, i.e., score at 24-hour, in addition to the score at 48-hour). This procedure was repeated until 9 induction applications of the active test article and of the placebo were made to one site each. The active control patch (i.e., Nitro-Dur® patch) was not applied during the induction phase.

Challenge phase (either Hercon's active/Hercon's placebo or Nitro-Dur®/Hercon's placebo)

Approximately two weeks after application of the last induction patches, challenge patches (the active test article and placebo or the active control and placebo) were applied to previously unpatched (virgin) sites, adjacent to the original induction patch sites. The patches were removed after 24 hours. The application sites were scored immediately post-removal and again 24 hours later. The subjects were asked to report any delayed reactions which might occur after the final patch readings (any?). For the protection of the test subjects at challenge, only one active patch and the placebo patch were applied during one 24 hour period (**Reviewer's note**: It is interesting to note that the nominal dosage for the active test article was 0.2 mg/hr and the dosage for the patches used in the bioequivalence study was 0.4 mg/hr.) The test scheme was as follows:

% Remaining Subjects	Monday (virgin sites)	Tuesday	Wednesday (new virgin sites)	Thursday	Friday
25%	A & B	Remove/Read	B & C	Remove/Read	Final Read
25%	B & A	Remove/Read	C & B	Remove/Read	Final Read
25%	C & B	Remove/Read	B & A	Remove/Read	Final Read
25%	B & C	Remove/Read	A & B	Remove/Read	Final Read

NOTE: Final readings were also performed on Wednesday for Monday patches prior to new application.

A = Hercon patch, B = Placebo patch, C = Nitro-Dur® patch
Using the above scheme, all subjects were applied all three articles, but only one nitroglycerin patch at a time.
[**Reviewer's note**: Initial readings were made 24 hours post application, i.e., immediately after patch removal. Final readings were made 24 hours after patch removal.]

Site and duration of patch application All application sites were washed with a residue-free soap (e.g., Ivory®) and water, and dried completely prior to application of any patches. Each patch was applied for 24 hours. The patch was applied to the inner aspect of both the upper arms of each subject. Following 24 hours of wear, the subjects returned to the clinic to have their patches evaluated for quality of wear. After removal of the patches, the sites were scored for residual adhesive and irritation.

Data analysis (Chi-square Analyses of Frequency)

Quality of wear (for overall condition and quality of adherence to the skin)

0 = Patch not present
1 = Practically falling off
2 = Approximately 3/4 of adhesive area loose
3 = Approximately 1/2 of adhesive area loose
4 = Approximately 1/4 of adhesive area loose
5 = Full adhesion observed

Residual adhesive (for any residual adhesive material that may or may not still be adhering to the skin following patch removal)

0 = None
1 = Slight
2 = Moderate
3 = Extensive

Skin Irritation (skin response/edema)

0 = No evidence of any effect
+ = (Barely perceptible) Minimal, faint, uniform or sporty erythema
1 = (Mild) Pink, uniform erythema covering all or most of the contact site
2 = (Moderate) Pink-red erythema uniform in the entire contact site
3 = (Marked) Bright-red erythema with/without petechiae or papules
4 = (Severe) Deep-red erythema with vesiculation or weeping

Edema at the test site was described according to the following scale:

0 = No edema
1 = (Barely perceptible) Very slight edema
2 = (Slight) Edges of area well defined by define raising
3 = (Moderate) Raised approximately 1 mm.
4 = (Severe) Raised more than 1 mm and extending beyond the area of exposure

Results

I. Induction phase

One hundred twenty (120) subjects enrolled in the study and 86 completed the study. The firm reported that thirty-four subjects discontinued due to either intolerable side effects or personal reasons unrelated to the conduct of the study.

Skin irritation scores (24-hour) The frequency of peak 24-hour erythema scores observed: (N=86)

Test Article	Induction Phase Peak Erythema Scores (24-hour)						
	0	+	1	2	3	4	N
Hercon NTS	2	6	43	34	1	0	86
Hercon Placebo	29	29	24	3	1	0	86

Based on the data, Hercon's nitroglycerin transdermal system exhibited significantly higher scores ($P<0.001$) than Hercon's placebo patch.

Skin irritation scores (48-hour) The frequency of peak 24-hour erythema scores observed: (N=86)

Test Article	Induction Phase Peak Erythema Scores (48-hour)						
	0	+	1	2	3	4	N
Hercon NTS	23	16	39	8	0	0	86
Hercon Placebo	52	13	18	3	0	0	86

Based on the data, Hercon's nitroglycerin transdermal system exhibited significantly higher scores ($P<0.001$) than Hercon's placebo patch.

Quality of Wear Scores (24-hour) The frequency of quality of wear scores recorded: (Data from discontinued subjects were used up to their point of discontinuation.)

Test Article	Induction Phase Quality of Wear Scores (24-hour)							
	5	4	3	2	1	0 (F)	0 (R)	N
Hercon NTS	598	52	11	8	5	40	46	760
Hercon Placebo	439	115	52	31	41	96	22	796

(F) = Panelist reported patch fell off
(R) = Panelist reported removal of the patch

Based on the data, Hercon's nitroglycerin transdermal system exhibited significantly better quality of wear (P<0.001) than Hercon's placebo patch.

Residual Adhesive Scores (24-hour) The frequency of residual adhesive scores recorded. Data from discontinued subjects were used up to their point of discontinuation.

Test Article	Induction Phase Residual Adhesive Scores (24-hour)				
	0	1	2	3	N
Hercon NTS	184	542	58	8	792
Hercon Placebo	583	213	2	0	798

Based on the data, Hercon's nitroglycerin transdermal system exhibited significantly higher residual adhesive (P<0.001) than Hercon's placebo patch.

Residual Adhesive Scores (48-hour) The frequency of residual adhesive scores recorded. Data from discontinued subjects were used up to their point of discontinuation.

Test Article	Induction Phase Residual Adhesive Scores (24-hour)				
	0	1	2	3	N
Hercon NTS	397	361	11	3	772
Hercon Placebo	723	53	0	0	776

Based on the data, Hercon's nitroglycerin transdermal system exhibited significantly higher residual adhesive (P<0.001) than Hercon's placebo patch.

II. Challenge Phase

A total of 86 subjects completed the challenge phase of the study. Observations of skin reaction were made at 24 and 48 hours post-application.

The following table summarizes the frequency of skin reactions observed at the 24-hour and 48-hour.

Test Article	Challenge Phase Erythema Scores (24-hour)						
	0	+	1	2	3	4	N
Hercon NTS	29	34	21	0	0	0	84
Hercon Placebo	77	5	2	0	0	0	84
Nitro-Dur®	20	46	17	2	0	0	85
Hercon Placebo	74	4	7	0	0	0	85

Both Hercon NTS and Nitro-Dur® patch exhibited significantly higher erythema scores than Hercon placebo patch (P<0.001). There was no significant difference between Hercon NTS and Nitro-Dur® patch.

Test Article	Challenge Phase Erythema Scores (48-hour)						
	0	+	1	2	3	4	N
Hercon NTS	80	2	3	0	0	0	85
Hercon Placebo	81	3	1	0	0	0	85
Nitro-Dur®	83	2	0	1	0	0	86
Hercon Placebo	81	3	2	0	0	0	86

There were no significant differences among the three test articles at the 48-hour reading.

Quality of Wear Scores(24-hour)

The following table summarizes the frequency of quality of wear scores recorded during the challenge phase of the study.

Test Article	Challenge Phase Quality of Wear Scores (24-hour)							
	5	4	3	2	1	0 (F)	0 (R)	N
Hercon NTS	57	7	5	2	2	5	6	84
Hercon Placebo	30	11	7	6	5	24	1	84
Nitro-Dur®	58	9	2	2	0	9	5	85
Hercon Placebo	24	9	6	9	12	24	1	85

(F) = Panelist reported patch fell off
(R) = Panelist reported removal of the patch

Both Hercon NTS and Nitro-Dur® patch exhibited significantly better 24-hour quality of wear scores than the placebo patch (P<0.001). There was no significant difference between Hercon NTS and Nitro-Dur® patch.

Residual Adhesive Scores (24-hour and 48-hour)

Test Article	Challenge Phase Residual Adhesive Scores (24-hour)				
	0	1	2	3	N
Hercon NTS	19	61	4	0	84
Hercon Placebo	69	15	0	0	84
Nitro-Dur®	17	64	4	0	85
Hercon Placebo	65	20	0	0	85

Test Article	Challenge Phase Residual Adhesive Scores (48-hour) 0	1	2	3	N
Hercon NTS	47	37	1	0	85
Hercon Placebo	80	5	0	0	85
Nitro-Dur®	39	44	3	0	86
Hercon Placebo	70	14	1	1	86

The placebo patch exhibited significantly less ($P<0.001$) residual adhesive than Hercon NTS and Nitro-Dur® patch at both 24-hour and 48-hour readings. There were no significant differences between Hercon NTS and Nitro-Dur® patch at either 24-hour or 48-hour readings.

Side effects The major reported side effects that were considered test article related included: headache (360 cases: 170 mild, 114 moderate, and 76 severe), nausea/upset stomach (25 cases), dizziness/light-headed (13 cases), vomiting (4 cases), and sting/burning at the patch site (4 cases). The firm did not report the comparative frequency of the side effects among the test articles.

Conclusion

The data observed in the challenge phase indicated that there were no significant differences in the erythema scores, in the quality of wear as defined in the study, and in the residual adhesive scores between Hercon's 0.2 mg/hr patch and Nitro-Dur 0.2 mg/hr.

The firm also concluded that under the conditions of a repeated insult patch test, the test article (Hercon's 0.2 mg/hr patch, Lot #E0692NG/488) was a low-grade irritant to human skin and was significantly more irritating than the placebo patch (Lot #G1102NGB/496)

Comments (to the bioequivalence study)

1. For nitroglycerin, the 90% confidence intervals for both Cmax and AUC were outside the acceptable range of 80-125%. [Hercon versus Transderm-Nitro: LN(Cmax), 106% -152% and LN(AUC0-24), 97%-130%, Hercon versus Key: LN(Cmax), 106%-152% and LN(AUC0-24), 101%-137%.] The AUC values for 1,2-dinitroglycerin, Hercon versus Key, were also outside the acceptable range of 80-125%.

2. There is a discrepancy in the number of data set reported in the mean data and the data used in the statistical analysis (ANOVA). Apparently, the firm used the data from all the subjects received each respective treatment in the mean data calculation (i.e., 32 received treatment A, 33 received treatment B, and 32 received treatment C). While in fact, only

30 subjects completed both treatments A and B, and 30 subjects completed both treatments A and C. The final statistical report showed 31 data sets for treatment A, apparently due to the inclusion of data from both subjects #3 and #19 (Note: Subject #19 did not receive treatment B and data from subject #3 after treatment C were stated as not evaluable due to the missing of samples between hr 9-24). In the future submission, the firm should be advised to report the results only from subjects who completed both test and reference products.

3. The data reported in the mean data calculation and in the variance analysis (ANOVA) are inconsistent. In the mean data calculation (see pages 306-308), the firm apparently treated those samples with assayed values less than the limit of quantitation (LOQ) as "missing" (see the count, N, in the mean data). While in the procedure of ANOVA, those samples with assayed values less than LOQ were reported as "zero". In the future submission, the firm should be advised to be consistent in the data presentation and to report those values less than LOQ as zero.

4. The firm described (on page 351) how the time to steady state was determined. Criterion 1 (requires no significant differences among the concentrations observed at each time point prior to the steady state time) appears to be in error. How would this affect the values of Cmax, Cmin, Cav, and the value of degree of fluctuation (DF) is not clear. For now, the determination of time to steady state would not affect the conclusion of the study.

5. The batch size of the test product was not reported.

6. The firm has determined the residual content of nitroglycerin in the used patches. The data, however, were not submitted.

7. It should be noted that each test patch was applied for 24 hours, which is different from the dosing schedule (i.e., to include a daily patch-off period of 10-12 hours) specified in the labeling of this drug product. In the future submission, the firm should be advised to apply the patch for 12-14 hours. The firm should be advised that an IND may be required for outside labeling use.

8. The drug release data were derived from 6 dosage units. The firm should be advised that <u>in vitro</u> dissolution (drug release) testing should be conducted on 12 individual units of the test and reference products and the summary report should include the raw, mean, range, and coefficient of variation data.

<u>Comments</u> (to the wear and repeated insult patch test)

9. Eighty-six (86) subjects completed the induction phase of the study. According to the study protocol, each subject received 24-hour patch applications three times a week (on Monday, Wednesday, and Friday) for three weeks and for each patch application the sites were scored at 24-hour and 48-hour. The irritation scores at 24-hour and 48-hour showed a total number of 86. It is not clear whether the scores reported were mean values. The firm should be advised to clarify. And if those were mean values, the firm should be advised to report the mean, range, and coefficient of variation of the data as well.

10. There is a discrepancy in the number of data set (i.e., N) reported in the challenged phase. The firm should be advised to clarify why N for the 48-hour score is more than that for the 24-hour score.

11. The firm has conducted the bioequivalence study on 0.4 mg/hr patch. While the wear and repeated insult patch study was conducted on 0.2 mg/hr patch. The firm should be advised that the observation made on the wear properties and the irritation potential of this study pertains only to the 0.2 mg/hr patch and the study does not establish that the larger patches have acceptable skin irritation characteristics.

Recommendation

The in vivo bioequivalence study conducted by Hercon Laboratories on its nitroglycerin transdermal patch, 0.4 mg/hr, Lot #Y0632NG/487, comparing it to Ciba's Transderm- Nitro®, 0.4 mg/hr, Lot #1M149250 and to Key's Nitro-Dur®, 0.4 mg/hr, Lot #D2212411 has been found unacceptable by the Division of Bioequivalence for the reason cited in comment #1.

The dissolution (drug release) testing conducted by Hercon Laboratories on its nitroglycerin transdermal patches, 0.2 mg/hr, Lot #E0692NG/488, 0.4 mg/hr, Lot #Y0632NG/487, and 0.6 mg/hr, Lot #E0762NG/489, is not acceptable for the reason cited in comment #8. Furthermore, the request for waiver of in vivo testing will not be considered until an acceptable in vivo bioequivalence study is conducted by the firm on this drug product.

The firm should be informed of the recommendation and comments #1-#11.

/S/

Yih-Chain Huang, Ph.D.
Division of Bioequivalence
Review Branch III

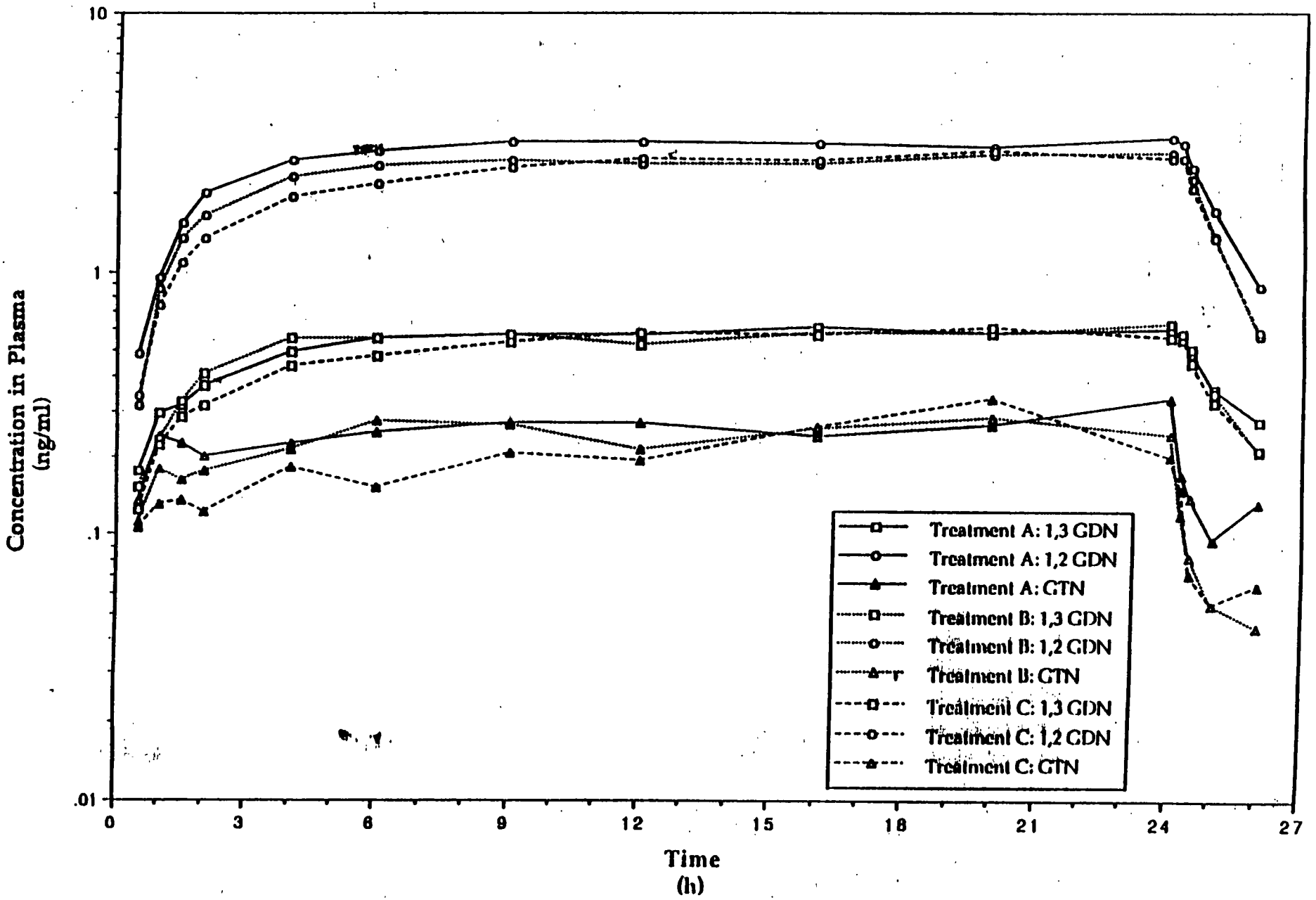
/S/

RD INITIALED MPark
FT INITIALED MPark

CONCUR /S/ Date 5/8/94

Ramakant M. Mhatre, Ph.D.
Acting Director
Division of Bioequivalence

cc: ANDA #89-885 (original, duplicate), HFD-600 (Hare), HFD-630, HFC-130 (JAllen), HFD-344 (CViswanathan), HFD-658 (Park, Huang), Drug File, Division File.


Nitroglycerin and Metabolite Mean Concentrations Over Time
Concentration in Plasma (ng/ml)
10
1
.1
.01
0
3
6
9
12
15
18
21
24
27
Time (h)
Treatment A: 1,3 GDN
Treatment A: 1,2 GDN
Treatment A: GTN
Treatment B: 1,3 GDN
Treatment B: 1,2 GDN
Treatment B: GTN
Treatment C: 1,3 GDN
Treatment C: 1,2 GDN
Treatment C: GTN